

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 April 2009 (23.04.2009)

PCT

(10) International Publication Number
WO 2009/050554 A2

(51) International Patent Classification:
A61K 31/519 (2006.01) *A61P 25/28* (2006.01)

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(21) International Application Number:
PCT/IB2008/002660

(22) International Filing Date: 6 October 2008 (06.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/981,168 19 October 2007 (19.10.2007) US

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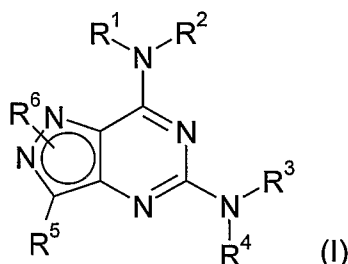
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, 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:

— without international search report and to be republished upon receipt of that report

(54) Title: TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS



(57) Abstract: The present invention provides for the use of PDE5 inhibitors in methods for treating in a mammal certain central nervous system (CNS) disorders or conditions, including neurodegenerative disorders such as for example Alzheimer's disease or stroke. This invention also pertains to the use of PDE5 inhibitors in methods for promoting in a mammal functional recovery following events such as stroke, such as coronary artery bypass grafting (CABG)-related stroke; craniocerebral trauma; traumatic brain injury; spinal cord trauma; cerebral ischemia, including cerebral ischemia related to CABG; multi-infarct dementia; post-CABG dementia; subdural hematoma; subarachnoid hemorrhage; or any of the wide varieties of brain tumors and/or their removal. The PDE5 inhibitors are compounds of formula (I) or tautomers thereof or pharmaceutically acceptable salts or solvates of said compounds or tautomers.



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TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

Field of the Invention

This invention pertains to the use of PDE5 inhibitors in methods for treating certain central nervous system (CNS) disorders or conditions, including neurodegenerative disorders such as for example Alzheimer's disease or stroke. This invention also pertains to the use of PDE5 inhibitors in methods for promoting functional recovery following events such as brain injury, craniocerebral trauma or stroke. This invention also pertains to the use of PDE5 inhibitors in methods for promoting neurorestoration, including neurorestoration following stroke, such as neurorestoration following coronary artery bypass grafting (CABG)-related stroke; neurorestoration following traumatic brain injury; neurorestoration following cerebral ischemia, including cerebral ischemia related to CABG; neurorestoration related to multi-infarct dementia; and neurorestoration related to post-CABG dementia.

Background of the Invention

PDE5A, is one of the superfamily of phosphodiesterases involved in the regulation by metabolic inactivation of the ubiquitous intracellular second messengers cAMP and cGMP. PDE5A is encoded by a single gene which in humans is located on chromosome 4q25-27 that is most highly expressed in smooth muscle, notably in the vasculature. The enzyme is specific for the metabolism of cGMP and, thus, regulates NO/cGMP-mediated vascular relaxation. Thus, pharmacological inhibition of PDE5A results in vascular smooth muscle relaxation caused by an increase in intracellular cGMP. These vascular relaxant effects of PDE5A inhibitors are the basis for the initial and continued interest in such compounds for the treatment of hypertension. However, it is the relaxation of smooth muscle in the corpus cavernosum of the penis, and the consequent facilitation of erection, that led to the first commercialization of PDE5A inhibitors for the treatment of male erectile dysfunction. Consistent with the high level of PDE5A expression in pulmonary vascular smooth muscle as well as endothelial cells, PDE5A inhibitors also

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reduce pulmonary vascular resistance. This has prompted the recent therapeutic use of these compounds to treat pulmonary hypertension.

In the mammalian central nervous system, the expression of PDE5A is restricted to cerebellar Purkinje neurons and neurons in the spinal cord, based on studies in rodents of PDE5A mRNA distribution by in situ hybridization and protein localization by immunohistochemistry (Nakamizo et al., Journal of Neuroscience Research 71:485–495 (2003); Kotera et al., The Journal of Histochemistry & Cytochemistry Volume 48(5): 685–693, 2000; Van Staveren et al., The Journal of Comparative Neurology 467:566–580 (2003)). In situ hybridization studies in human brain (Reyes-Irisarri et al., European Journal of Neuroscience, Vol. 25, pp. 3332–3338, 2007) indicate essentially the same distribution pattern. In contrast to the paucity of PDE5A expression in the brain parenchyma, the enzyme is highly expressed in the cerebrovasculature. Despite the relatively restricted neuronal distribution of PDE5A, there have nonetheless been a number of reports indicating that PDE5A inhibitors effect brain activity. PDE5A inhibitors are reported to improve performance in a number of animal models of memory retention and also affect the re-entrainment of circadian rhythms (Patricia V. Agostino, Santiago A. Plano, and Diego A. Golombek, "Sildenafil accelerates reentrainment of circadian rhythms after advancing light schedules," PNAS 2007). It has also been observed that PDE5A inhibitors improve functional recovery after stroke (middle cerebral artery occlusion; MCA-o) in rodents (Zhang et al., Stroke, 2002; 33:2675-2680 and Zhang et al., Stroke, 2005; 36:847-852) even if the initiation of treatment is delayed for several days after infarction. Since in rodents the extent of infarction after MCA-o stabilizes well within the first 24 h after MCA-o, there is no effect of the PDE5A inhibitors on infarct volume under these delayed dosing regimens. This has engendered the hypothesis that the effect of PDE5A inhibition on functional recovery after stroke results from an effect on the functional reorganization of the brain following acute ischemic brain injury.

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Stroke is the leading cause of serious long term disability in the United States. Despite massive effort over the last 20 years, the only available therapy that has an effect on the extent of disability is acute treatment with thrombolytic agents such as tPA. However, these agents are effective only if
5 administered in the hours immediately after stroke and carry a risk of cerebral hemorrhage. Consequently, the use of thrombolytics is limited to only a few percent of the more than 700,000 individuals that suffer a stroke in the United States each year. This invention posits the use of PDE5A inhibitors in this regard. There is an extensive clinical experience with PDE5A inhibitors in the
10 treatment of male erectile dysfunction, and more recently in pulmonary hypertension, that suggests that such compounds are generally well tolerated, including in populations with vascular disease. Furthermore, PDE5A inhibitors are effective at promoting recovery of function after stroke even when administered well after the acute phase of the attack, significantly increasing
15 the feasibility of treating a much larger percentage of patients than has been possible with thrombolytic therapy. Thus, PDE5A inhibitors may represent a relatively safe and effective new therapeutic approach to the treatment of stroke.

Inhibitors of PDE5 have been reported in several chemical classes,
20 including: pyrazolo[4,3-d]pyrimidin-7-ones (e.g. Int'l Publications WO 93/06104, WO 98/49166, WO 99/54333, WO 00/24745, WO 01/27112, and WO 01/27113); pyrazolo[3,4-d]pyrimidin-4-ones (e.g. Int'l Publication WO 93/07149); pyrazolo[4,3-d]pyrimidines (e.g. International Publication WO 01/18004); quinazolin-4-ones (e.g. Int'l Publication WO 93/12095); pyrido[3,2-
25 d]pyrimidin-4-ones (e.g. Int'l Publication WO 94/05661); purin-6-ones (e.g. Int'l Publication WO 94/00453); hexahydropyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-diones (e.g. Int'l Publication WO 95/19978) and imidazo[5,1-f][1,2,4]triazin-ones (e.g. Int'l Publication WO 99/24433). International Publications WO 02/00660 and WO 01/18004 discuss pyrazolo[4,3-
30 d]pyrimidines with a PDE-5 inhibiting effect, which can be used for treating disorders of the cardiovascular system. US 7,135,498 and US 2002-0155173

generally describe the use of PDE5 inhibitors in models of neurological disorders.

Summary of the Invention

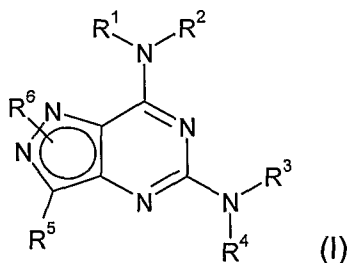
The present invention provides for the use of PDE5 inhibitors in
5 methods for treating in a mammal certain central nervous system (CNS)
disorders or conditions, including neurodegenerative disorders such as for
example Alzheimer's disease or stroke. This invention also pertains to the
use of PDE5 inhibitors in methods for promoting neurorestoration in a
mammal, including neurorestoration following stroke, such as
10 neurorestoration following coronary artery bypass grafting (CABG)-related
stroke; neurorestoration following craniocerebral trauma; neurorestoration
following traumatic brain injury; neurorestoration following spinal cord trauma;
neurorestoration following cerebral ischemia, including cerebral ischemia
related to CABG; neurorestoration related to multi-infarct dementia;
15 neurorestoration related to post-CABG dementia; neurorestoration following
subdural hematoma; neurorestoration following subarachnoid hemorrhage; or
neurorestoration following any of the wide varieties of brain tumors and/or
their removal. This invention also pertains to the use of PDE5 inhibitors in
methods for promoting in a mammal functional recovery following events such
20 as stroke, such as coronary artery bypass grafting (CABG)-related stroke;
craniocerebral trauma; traumatic brain injury; spinal cord trauma; cerebral
ischemia, including cerebral ischemia related to CABG; multi-infarct dementia;
post-CABG dementia; subdural hematoma; subarachnoid hemorrhage; or any
of the wide varieties of brain tumors and/or their removal. This invention also
25 pertains to the use of PDE5 inhibitors in the manufacture of medicaments for
promoting in a mammal functional recovery following events such as stroke,
such as coronary artery bypass grafting (CABG)-related stroke; craniocerebral
trauma; traumatic brain injury; spinal cord trauma; cerebral ischemia,
including cerebral ischemia related to CABG; multi-infarct dementia; post-
30 CABG dementia; subdural hematoma; subarachnoid hemorrhage; or any of
the wide varieties of brain tumors and/or their removal.

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This invention also pertains to the use of PDE5 inhibitors in methods for promoting functional recovery in a mammal afflicted with chronic conditions, such as Alzheimer's disease, Parkinson disease, VaD, other dementia syndromes, Multiple Sclerosis, Parkinsons, ALS, Huntington's Disease, fronto-temporal dementias, Lewy-body diseases, and metabolic disorders such as diabetes and hyperammonimnia.

The PDE5 inhibitors used in the invention may be administered alone or in combination with other therapeutic agents, such as symptomatic and/or disease modifying agents.

The PDE5 inhibitors used in the invention are compounds of formula (I)



wherein

R^1 is a cyclic group selected from R^A , R^B , R^0 and R^D , each of which is optionally substituted with one or more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 and R^4 are each independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl or C_3 - C_{10} cycloalkyl, each of which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups, or hydrogen;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^5 is selected from $-Y-CO_2R^{15}$ and $-Y-R^{16}$;

R^6 , which may be attached at N^1 or N^2 , is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl, each of which is optionally substituted by C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or a cyclic group selected from R^J , R^K , R^L and R^M , or R^6 is R^N , C_3 - C_7 cycloalkyl or C_3 - C_7 halocycloalkyl, each of which is optionally substituted by C_1 - C_6 alkoxy or C_1 - C_6 haloalkoxy, or R^6 is hydrogen;

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R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$,
5 $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN, C_3 - C_6 cycloalkyl, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} ,
10 $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN, oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6
15 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{15} is hydrogen or C_1 - C_6 alkyl optionally substituted with one or more groups selected from phenyl, halo, OH, C_1 - C_6 alkyloxy, NH_2 , $NH(C_1$ - C_6 alkyl) and $N(C_1$ - C_6 alkyl)₂;

20 R^{16} is a carboxylic acid isostere selected from tetrazol-5-yl, 5-trifluoromethyl-1,2,4-triazol-3-yl, 5-(methylsulfonyl)-1,2,4-triazol-3-yl, 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl, $-SO_2NHR^{17}$ and $-CONHR^{18}$;

R^{17} is selected from C_1 - C_6 alkyl, phenyl, $-CO-(C_1$ - C_6 alkyl) and $-CO$ -phenyl;

25 R^{18} is selected from $-SO_2-(C_1$ - C_6 alkyl) and $-SO_2$ -phenyl;

R^A and R^J are each independently a C_3 - C_{10} cycloalkyl or C_3 - C_{10} cycloalkenyl group, each of which may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and which may be fused to either (a) a monocyclic aromatic ring selected from a benzene ring and a 5-
30 or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or (b) a 5-, 6- or 7-membered

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heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^B and R^K are each independently a phenyl or naphthyl group, each of which may be fused to (a) a C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl ring, (b) a
5 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or (c) a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^C , R^L and R^N are each independently a monocyclic or, when there are
10 an appropriate number of ring atoms, polycyclic saturated or partly unsaturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which ring may be fused to a C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl group or a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-
15 membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^D and R^M are each independently a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur, which ring may further be fused to (a) a second 5- or 6-
20 membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur; (b) C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl ring; (c) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur; or (d) a benzene ring;

25 R^E , R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to three
30 heteroatoms independently selected from nitrogen, oxygen and sulphur; and

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Y is a covalent bond, $-\text{CH}_2\text{-O-CH}_2-$, $\text{C}_1\text{-C}_6$ alkylene or $\text{C}_3\text{-C}_7$ cycloalkylene;

a tautomer thereof or a pharmaceutically acceptable salt or solvate of said compound or tautomer.

5 The present invention also provides for a composition comprising the PDE5 inhibitors disclosed herein for treating in a mammal certain central nervous system (CNS) disorders or conditions, including neurodegenerative disorders such as for example Alzheimer's disease or stroke. This invention also pertains to a composition comprising the PDE5 inhibitors disclosed
10 herein for promoting in a mammal functional recovery following events such as brain injury, craniocerebral trauma or stroke. This invention also pertains to a composition comprising the PDE5 inhibitors disclosed herein for promoting neurorestoration in a mammal, including neurorestoration following stroke, such as neurorestoration following coronary artery bypass grafting
15 (CABG)-related stroke; neurorestoration following traumatic brain injury; neurorestoration following cerebral ischemia, including cerebral ischemia related to CABG; neurorestoration related to multi-infarct dementia; and neurorestoration related to post-CABG dementia.

As used herein, alkylene indicates an alkyl-*m,n*-diyl unit where *m* and *n*
20 are the same or different, such as methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$) and propane-1,2-diyl ($-\text{CH}(\text{CH}_3)\text{CH}_2-$).

As used herein, cycloalkylene indicates a cycloalkyl-*m,n*-diyl unit where *m* and *n* are the same or different, such as cyclopropane-1,1-diyl and cyclohexane-1,4-diyl.

25 Unless otherwise indicated, an alkyl or alkoxy group may be straight or branched and contain 1 to 8 carbon atoms, preferably 1 to 6 and particularly 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, pentyl and hexyl. Examples of alkoxy include methoxy, ethoxy, isopropoxy and n-butoxy.

30 Unless otherwise indicated, an alkenyl or alkynyl group may be straight or branched and contain 2 to 8 carbon atoms, preferably 2 to 6 and

particularly 2 to 4 carbon atoms and may contain up to 3 double or triple bonds which may be conjugated. Examples of alkenyl and alkynyl include vinyl, allyl, butadienyl and propargyl.

Unless otherwise indicated, a cycloalkyl or cycloalkyloxy group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl and adamantyl.

Unless otherwise indicated, a cycloalkenyl group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and may contain up to 3 double bonds. Examples of cycloalkenyl groups are cyclopentenyl and cyclohexenyl.

Aryl includes phenyl, naphthyl, anthracenyl and phenanthrenyl.

Unless otherwise indicated, a heteroalicycyl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated or partially unsaturated. Examples of heteroalicycyl groups are oxiranyl, azetidiny, tetrahydrofuranyl, thiolanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, sulfolanyl, dioxolanyl, dihydropyranyl, tetrahydropyranyl, piperidinyl, pyrazolinyl, pyrazolidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, azepinyl, oxazepinyl, thiazepinyl, thiazolinyl and diazapanyl.

Unless otherwise indicated, a heteroaryl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur. Examples of heteroaryl groups are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, triazinyl. In addition, the term heteroaryl includes fused heteroaryl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

Halo means fluoro, chloro, bromo or iodo.

Haloalkyl includes monohaloalkyl, polyhaloalkyl and perhaloalkyl, such as 2-bromoethyl, 2,2,2-trifluoroethyl, chlorodifluoromethyl and trichloromethyl.

Haloalkoxy includes monohaloalkoxy, polyhaloalkoxy and
5 perhaloalkoxy, such as 2-bromoethoxy, 2,2,2-trifluoroethoxy, chlorodifluoromethoxy and trichloromethoxy. Halocycloalkyl includes monohalocycloalkyl, polyhalocycloalkyl and perhalocycloalkyl.

Unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from
10 a number of alternative groups, the selected groups may be the same or different.

In one preferred embodiment, R^1 is R^A , which is optionally substituted with one or more R^7 groups; and R^A is a C_3 - C_{10} cycloalkyl group, which may be either monocyclic or, when there are an appropriate number of ring atoms,
15 polycyclic, which may be fused to either (a) a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or (b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur.

20 Preferably, R^A is a monocyclic C_3 - C_8 cycloalkyl group.

More preferably, R^A is a monocyclic C_5 - C_7 cycloalkyl group.

Most preferably, R^A is cyclopentyl or cyclohexyl.

In another preferred embodiment, R^1 is R^B , which is optionally substituted with one or more R^7 groups.

25 Preferably, R^B is phenyl.

In another preferred embodiment, R^1 is R^C , which is optionally substituted with one or more R^7 groups.

Preferably, R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a
30 heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^C is a monocyclic saturated or partly unsaturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

Most preferably, R^C is a monocyclic saturated ring system containing
5 between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

In another preferred embodiment, R^1 is R^D , which is optionally substituted with one or more R^7 groups.

Preferably, R^D is a 5- or 6-membered heteroaromatic ring containing up
10 to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

More preferably, R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring
15 including 1, 2 or 3 nitrogen atoms.

More preferably R^D is furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

Most preferably, R^D is pyrazolyl, imidazolyl, isoxazolyl, oxazolyl,
20 oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

Preferably, R^7 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$.

More preferably, R^7 is halo, C_1-C_3 alkyl, C_1-C_3 alkoxy, hydroxy or $CONH(C_1-C_3 \text{ alkyl})$.

25 Most preferably, R^7 is fluoro, methyl, ethyl, hydroxy, methoxy, propoxy or $CONHMe$.

Preferably, R^2 is hydrogen or methyl.

More preferably, R^2 is hydrogen.

Preferably, R^3 is hydrogen, C_1-C_6 alkyl, which is optionally substituted
30 with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic or, when there are an

appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

In one preferred embodiment, R^3 is R^E , which is optionally substituted with one or more R^9 groups and wherein R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom.

More preferably, R^E is azetidiny, pyrrolidinyl or piperidinyl.

In another preferred embodiment, R^3 is C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups and wherein R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.

More preferably, R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, $NMeCO_2^tBu$, CO_2H , $CONHMe$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.

In one preferred embodiment, R^8 is R^G , which is optionally substituted with one or more R^9 groups and wherein R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom and optionally one oxygen atom.

Most preferably, R^G is pyrrolidinyl, piperidinyl or morpholinyl.

In another preferred embodiment, R^8 is R^H , which is optionally substituted with one or more R^9 groups and wherein R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms.

More preferably, R^H is pyrazolyl.

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Preferably, R^9 is methyl or CO_2^tBu .

In another preferred embodiment, R^3 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl, which is optionally substituted with one or more R^8 groups, or R^3 is azetidiny, pyrrolidiny or piperidiny, each of which is optionally substituted with one or
5 more R^9 groups, wherein R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , NHMe , NMe_2 , NHCO_2^tBu , $\text{NMeCO}_2^t\text{Bu}$, CO_2H , CONHMe , pyrrolidiny, piperidiny, morpholiny or pyrazolyl, the last four of which are optionally substituted with one or more R^9 groups and wherein R^9 is methyl or CO_2^tBu .

In one preferred embodiment, R^4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$
10 haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkynyl.

More preferably, R^4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ haloalkyl.

Most preferably, R^4 is hydrogen, methyl or ethyl.

In another preferred embodiment, $-\text{NR}^3\text{R}^4$ forms R^F , which is optionally substituted with one or more R^{10} groups and wherein R^F is a monocyclic or,
15 when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur.

More preferably, R^F is a monocyclic or, when there are an appropriate
20 number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing one or two nitrogen atoms and optionally one other atom selected from oxygen and sulphur.

Most preferably, R^F is selected from azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, 3-azabicyclo[3.1.0]hex-3-yl, homopiperaziny,
25 2,5-diazabicyclo[4.3.0]non-2-yl, 3,8-diazabicyclo[3.2.1]oct-3-yl, 3,8-diazabicyclo[3.2.1]oct-8-yl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 1,4-diazabicyclo[4.3.0]non-4-yl and 1,4-diazabicyclo[3.2.2]non-4-yl.

Preferably R^{10} is halo, OR^{12} , $\text{NR}^{12}\text{R}^{13}$, $\text{NR}^{12}\text{CO}_2\text{R}^{14}$, CO_2R^{13} , oxo, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ haloalkyl, the last two of which are optionally substituted by
30 R^{11} .

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More preferably, R^{10} is halo, methyl, ethyl, isopropyl, hydroxy, methoxy, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, CO_2H , CO_2^tBu , oxo, benzyl, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2 or $-CH_2NMeCO_2^tBu$.

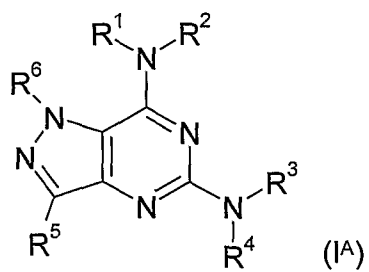
In one preferred embodiment, R^5 is $-Y-CO_2R^{15}$.

- 5 In one preferred embodiment, R^{15} is hydrogen or C_1-C_6 alkyl optionally substituted with one or more groups selected from halo, OH, C_1-C_6 alkyloxy, NH_2 , $NH(C_1-C_6alkyl)$ and $N(C_1-C_6alkyl)_2$. Preferably R^{15} is hydrogen or C_1-C_3 alkyl. More preferably R^{15} is hydrogen.

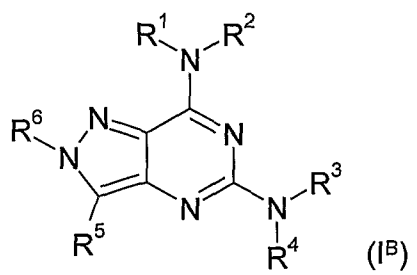
In another preferred embodiment, R^{15} is C_1-C_6 -alkyl or benzyl.

- 10 Preferably Y is a covalent bond or C_1-C_6 alkylene. More preferably, Y is a covalent bond or methylene. Most preferably Y is a covalent bond. In another preferred embodiment, R^5 is $-Y-R^{16}$. Preferably R^{16} is a carboxylic acid isostere selected from $-CONHR^{18}$, tetrazol-5-yl and 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl. Preferably Y is a covalent bond or C_1-C_6 alkylene. More preferably, Y is a covalent bond or methylene.

15 Preferably, R^6 is positioned on N^1 to give the compound of formula (I^A):



In an alternative embodiment of the present invention, R^6 may be positioned on N^2 to give the compound of formula (I^B):



20

In the compounds of formulas (I), (I^A), and (I^B), preferably R^6 is C_1-C_6 alkyl or C_1-C_6 haloalkyl, each of which is optionally substituted by C_1-C_6

alkoxy, C₁-C₆ haloalkoxy or a cyclic group selected from R^J, R^L and R^M, or R⁶ is R^N or hydrogen;

R^J is a C₃-C₇ monocyclic cycloalkyl group;

R^L and R^N are each independently a monocyclic, saturated or partly
5 unsaturated ring system containing between 4 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and

R^M is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

More preferably, R⁶ is C₁-C₄ alkyl or C₁-C₄ haloalkyl, each of which is
10 optionally substituted by C₁-C₄ alkoxy, C₁-C₄ haloalkoxy or a cyclic group selected from R^J, R^L and R^M, or R⁶ is R^N or hydrogen;

R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom
15 selected from nitrogen, oxygen and sulphur; and

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur.

In other preferred embodiments, R⁶ is C₁-C₄ alkyl or C₁-C₄ haloalkyl, each of which is optionally substituted by C₁-C₄ alkoxy or a cyclic group
20 selected from R^J, R^L and R^M, or R⁶ is R^N or hydrogen;

R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms containing one heteroatom selected from nitrogen, oxygen and sulphur; and

25 R^M is a 5- or 6-membered heteroaromatic ring containing one nitrogen atom.

More preferably, R⁶ is C₁-C₄ alkyl or C₁-C₄ haloalkyl, each of which is optionally substituted by C₁-C₄ alkoxy, cyclopropyl, cyclobutyl, tetrahydrofuranyl, tetrahydropyranyl or pyridinyl, or R⁶ is hydrogen or
30 tetrahydropyranyl.

Most preferably, R^6 is hydrogen, methyl, ethyl, isopropyl, isobutyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, propoxyethyl, 2,2,2-trifluoroethyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl or pyridinylmethyl.

5 Preferred embodiments of compounds of formula (I) are those that incorporate two or more of the foregoing preferences.

In some embodiments of this invention, R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

10 R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

15 or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^5 is $-Y-CO_2R^{15}$ or $-Y-R^{16}$;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from

20 R^J , R^L and R^M , or R^6 is R^N or hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN ;

25 R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

30 R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

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R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

5 R^A is a monocyclic C_3 - C_8 cycloalkyl group;

R^B is phenyl;

R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

10 R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

15 R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

20 R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

25 R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond or C_1 - C_6 alkylene.

In other embodiments of this invention, R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or
30 more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

5 or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^5 is $-Y-CO_2R^{15}$ or $-Y-R^{16}$;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN ;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

25 R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{15} is hydrogen or C_1 - C_3 alkyl;

R^{16} is tetrazol-5-yl, 5-trifluoromethyl-1,2,4-triazol-3-yl or 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl;

R^A is a monocyclic C_3 - C_8 cycloalkyl group;

30 R^B is phenyl;

R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

5 R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

10 R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

15 R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

20 R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond or C_1 - C_6 alkylene.

In some more preferred embodiments of this invention, R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

25 R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

30 R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;
or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

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R^5 is $-Y-CO_2R^{15}$;

R^6 is C_1-C_4 alkyl or C_1-C_4 haloalkyl, each of which is optionally substituted by C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

5 R^7 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$;

R^8 is halo, phenyl, C_1-C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1-C_6 alkyl, C_1-C_6 haloalkyl or CO_2R^{12} ;

10 R^{10} is halo, C_3-C_{10} cycloalkyl, C_3-C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN, oxo, C_1-C_6 alkyl or C_1-C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

15 R^{12} and R^{13} are each independently hydrogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^{14} is C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^A is a monocyclic C_5-C_7 cycloalkyl group;

R^B is phenyl;

20 R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further
25 nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom;

30 R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring

atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur;

R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond or methylene.

In other more preferred embodiments of this invention, R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^5 is $-Y-CO_2R^{15}$;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

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R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN, oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{15} is hydrogen;

R^A is a monocyclic C_5 - C_7 cycloalkyl group;

R^B is phenyl;

R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom;

R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur;

R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms;

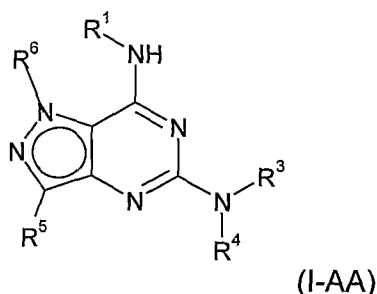
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R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom
5 selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond or methylene.

In an alternative embodiment, the present invention provides compounds of formula (I-AA)



10 wherein

R^1 is a pyridyl optionally substituted with one or more C_1 - C_6 alkyl groups;

R^3 and R^4 are each independently hydrogen or C_1 - C_6 alkyl;

R^5 is $-\text{CONHR}^{18}$;

15 R^6 is C_1 - C_6 alkyl, optionally substituted by a substituent selected from $-\text{OH}$, C_3 - C_6 cycloalkyloxy, C_1 - C_6 alkoxy and C_1 - C_6 haloalkoxy;

R^{18} is selected from the group consisting of $-\text{SO}_2$ -(C_1 - C_6 alkyl) and $-\text{SO}_2$ -phenyl; and tautomers thereof or a pharmaceutically acceptable salts, or solvates of said compounds or tautomers.

20 In one embodiment of the compounds of formula I-AA, R^1 is 2-pyridinyl substituted with one or more methyl. In another embodiment of the compounds of formula I-AA, R^3 and R^4 are independently selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In another embodiment of the compounds of formula I-AA, R^{18} is selected from the group
25 consisting of $-\text{SO}_2\text{CH}_3$ and $-\text{SO}_2\text{CH}_2\text{CH}_3$. In another embodiment of the compounds of formula I-AA, R^6 is ethyl, optionally substituted by a substituent

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selected from the group consisting of hydroxyl, methoxy, ethoxy, propoxy, fluoromethoxy, fluoroethoxy, fluoropropoxy, difluoromethoxy, difluoroethoxy, difluoropropoxy, trifluoromethoxy, trifluoroethoxy, trifluoropropoxy, and cyclobutyloxy.

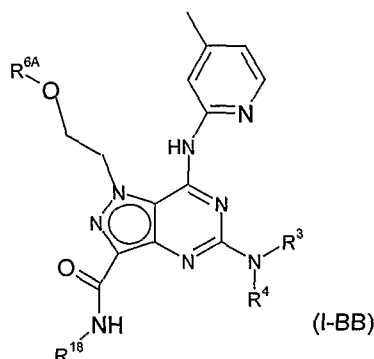
5 In another embodiment of the compounds of formula I-AA, R¹ pyridinyl is substituted with one or more methyl;

R³ and R⁴ are independently selected from the group consisting of hydrogen, methyl, ethyl, propyl and isopropyl;

R⁶ is ethyl, optionally substituted by a substituent selected from the
10 group consisting of -OH, C₃-C₆ cycloalkyloxy, C₁-C₆ alkoxy and C₁-C₆ haloalkoxy; and

R¹⁸ is selected from the group consisting of -SO₂CH₃ and -SO₂CH₂CH₃.

15 In another alternative embodiment of the present invention, the present invention provides compounds of formula (I-BB)



wherein

R³ and R⁴ are each independently selected from the group consisting of methyl, ethyl, and isopropyl;

20 R^{6A} is selected from the group consisting of methyl, ethyl, propyl, fluoromethyl, fluoroethyl, fluoropropyl, difluoroethyl, difluoropropyl, trifluoroethyl, and trifluoropropyl; and

R¹⁸ is selected from the group consisting of -SO₂CH₃, and -SO₂CH₂CH₃.

25 Most preferred compounds are:

- methyl 5-((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
methyl 1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylanino)-7-(6-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
5 ethyl 1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
2-(dimethylanino)ethyl 5-dimethylanino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
1-(2-ethoxyethyl)-5-(*N*-methyl-*N*-propylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
10 5-(*N*-isopropyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1-(2-propoxy-ethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
7-(4,6-dimethylpyridin-2-ylamino)-1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methyl-amino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
15 5-(*N*-cyclobutyl-*N*-methylanino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-ethoxyethyl)-5-isopropylanino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(2-methoxypyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
20 3-[1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]-2*H*-1,2,4-oxadiazol-5-one,
3-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]-2*H*-1,2,4-oxadiazol-5-one,
25 1-(2-ethoxyethyl)-7-(4-fluoro-3-methylphenylanino)-5-(*N*-isopropyl-*N*-methylanino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(4-fluoro-3-methylphenylanino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
7-(3,4-dimethylphenylanino)-1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
30 1-(2-(cyclopropylmethoxy)ethyl)-5-(*N*-isopropyl-*N*-methylanino)-7-(4-

methyl-pyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-(cyclopropylmethoxy)ethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methyl-pyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
5 1-(2-isopropoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
N-[1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide, and
10 N-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide, and
tautomers thereof and pharmaceutically acceptable salts or solvates of said compounds or tautomers.

Pharmaceutically acceptable salts of the compounds of this invention
15 include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate,
20 hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate,
25 tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

30 For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH,

Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of the compounds this invention may be readily prepared by mixing together solutions of the compounds and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of formula I may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention is the method of treatment comprising administering a complex such as a clathrate, a drug-host inclusion complex wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included is the method of treatment comprising administering a complex of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblan (August 1975).

Hereinafter all references to the compounds of formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The invention includes is the method of treatment comprising administering compounds of formula (I) as hereinbefore defined, prodrugs, or isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

Also within the scope of the invention is the method of treatment comprising administering a so-called 'prodrug' of a compound of formula (I). Thus certain derivatives of compounds of formula (I) which may have little or

no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in

5 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of

10 formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality

15 (-COOH), an ester thereof, for example, replacement of the hydrogen with (C₁-C₈)alkyl; (ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C₁-C₆)alkanoyloxymethyl; and (iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR

20 where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C₁-C₁₀)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

25 Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

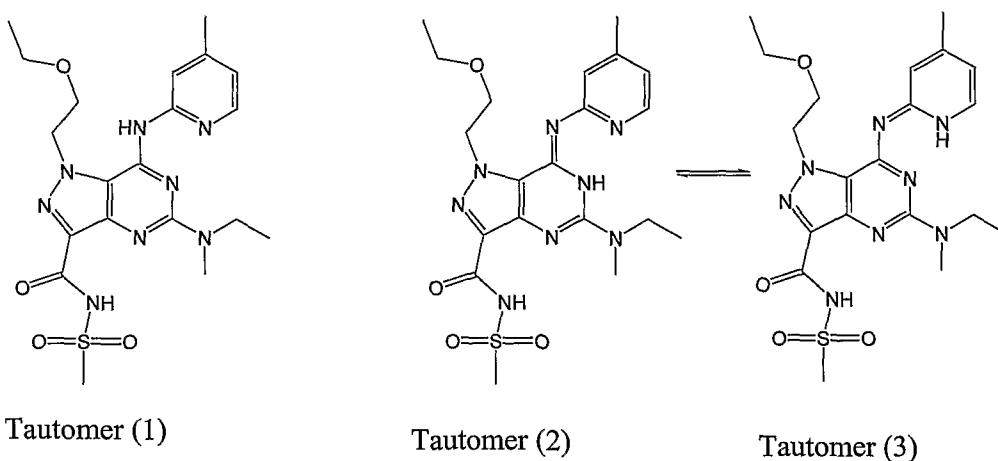
Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or *Z/E*)

30 isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can

occur. It follows that a single compound may exhibit more than one type of isomerism.

Three forms of a representative compound of formula I, N-[1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide (hereinafter "compound A"), have been identified. Compound A is Example 115 of US-2005-0245544-A1 and can be prepared by the methods disclosed therein. As explained in greater detail below, the three forms - Form A, Form B and Form C - each have distinct physical properties relative to each other.

As used in this application, the nomenclature "N-[1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide" is intended to embrace all tautomeric isomers of N-[1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide. For example, three tautomeric isomers of N-[1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide are shown below as Tautomer (1), Tautomer (2) and Tautomer (3). These tautomers can be prepared as disclosed in WO 2006/120552.



Without being held to a particular theory, it is hypothesized that Form A crystallizes as Tautomer (1) above, Form B as Tautomer (2), and Form C as

Tautomer (3) above. These forms differ in the location of a nitrogen-bound hydrogen atom.

Included within the scope of the present invention is the method of treatment comprising administering any stereoisomer, geometric isomer and
5 tautomeric form of a compound of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

10 *Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor
15 or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an
20 acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

25 Chiral compounds of formula I (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine,
30 typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

5 The present invention includes is the method of treatment comprising administering any pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

10 Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

15 Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

20 Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

25 Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

30 Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone, d₆-DMSO.

The term "treatment" includes palliative, curative and prophylactic
5 treatment.

In a further aspect, the present invention provides for the use of a compound of formula (I), or a tautomer, salt or solvate thereof, for the manufacture of a medicament for the treatment of the condition disclosed herein.

10 The present invention is the method of treatment comprising administering the compounds of formula I alone or in combination with other therapeutic agents. When used in combination with another therapeutic agent the administration of the two agents may be simultaneous or sequential. Simultaneous administration includes the administration of a single dosage
15 form that comprises both agents and the administration of the two agents in separate dosage forms at substantially the same time. Sequential administration includes the administration of the two agents according to different schedules provided that there is an overlap in the periods during which the treatment is provided. Suitable agents with which the compounds
20 of formula (I) can be co-administered include aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), C11027, CCR5
25 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone
30 receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas

(such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin,
5 [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0] hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1 α ,3 α ,5 α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-
10 5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid).

The compounds of formula (I) may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof).
15 Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and
20 stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical
25 Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds of formula I may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

30 Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders,

lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs.

5 Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

10 The compounds of formula I may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60
15 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose,
20 starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin,
25 sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and
30 dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the
5 tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the
10 tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2
15 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final
20 formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

25 Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release
30 technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line,

25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds of formula I may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting

powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers
5 may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

10 Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of formula I can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture,
15 for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable
20 propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention
25 comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug
30 product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting

method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and
5 cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran,
10 glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of
15 formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations
20 of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

25 In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1µg to 20mg of the compound of formula (I). The overall daily dose will typically be in the range 1µg to 80mg which may be
30 administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of formula I may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

- 5 Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

 The compounds of formula I may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or
10 solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid,
15 polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

- 20 Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

 The compounds of formula I may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof
25 or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

 Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and
30 non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary

additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in Int'l Publications WO 91/11172, WO 94/02518, and WO 98/55148.

5 It is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound of formula I, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

10 Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of this invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

15 The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called
20 memory aid.

 For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.1mg to 500 mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1 mg to 500 mg, while
25 an intravenous dose may only require from 0.01mg to 50mg. The total daily dose may be administered in single or divided doses.

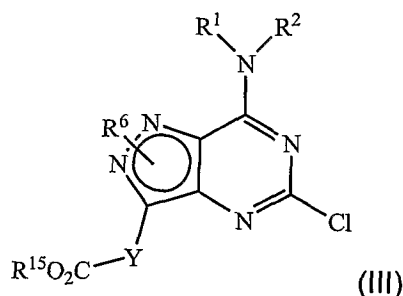
 These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and
30 the elderly.

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Compounds of formula I may be prepared, in known manner in a variety of ways. Examples of such ways are disclosed in US 2005-024554A1, which is incorporated by reference herein in its entirety.

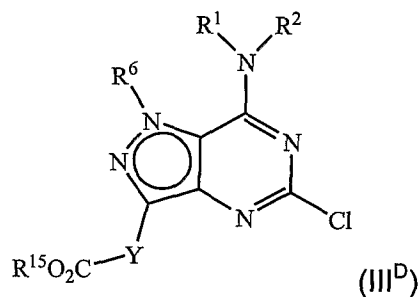
The following compounds (and salts thereof) form further aspects of
5 the compounds of formula I:

A compound of formula (III)



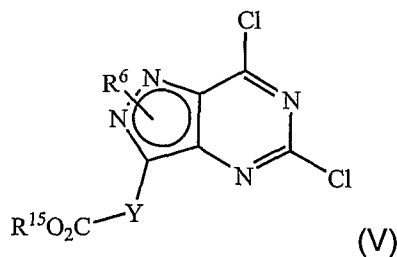
wherein R^1 , R^2 , R^6 , R^{15} and Y are as defined above. In some embodiments, R^{15} is C_1 - C_6 -alkyl or benzyl.

10 Preferred is a compound of formula (IIID)



wherein R^1 , R^2 , R^6 , R^A and Y are as defined above. In some embodiments, R^{15} is C_1 - C_6 -alkyl or benzyl.

A compound of formula (V)

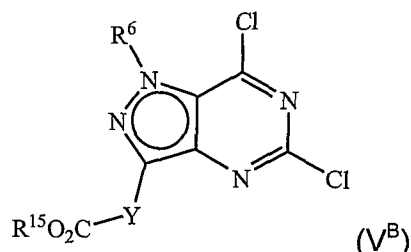


15

wherein R^6 , R^A and Y are as defined above. In some embodiments, R^{15} is C_1 - C_6 -alkyl or benzyl.

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Preferred is a compound of formula (VB)



wherein R⁶, R^A and Y are as defined above.

The compounds of formula I are further illustrated by the non-limiting
 5 examples disclosed in US 2005-0245544A1, which is incorporated by
 reference herein in its entirety.

The benefit of the compounds of the invention is illustrated by the
 following examples, which are not intended to limit the invention in any way.

Methods and Materials

10 The following experiments were designed to show the efficacy of the
 compound of formula I to promote stroke recovery in rats after middle cerebral
 artery occlusion (MCA-o). Male, Sprague-Dawley rats weighing ~ 300g at the
 start of experimentation were grouped in groups of ten each. MCA-o was
 achieved using a modified Tamura protocol as further disclosed below.

15 To promote stroke recovery, a first group of rats was treated with *N*-[1-
 (2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-
 pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide ("compound A"), a
 representative compound of formula I. This compound was administered
 twice a day by subcutaneous route at 10 mg/kg, starting 24 h after MCA-o and
 20 continued for 7 days.

A second group of rats was instead treated with a vehicle.

As is further disclosed below, the outcome of the treatment was
 measured using the following parameters: Body weight, Hind limb placement,
 Forelimb placement and Body Swing test. Assessments are to be made at 3,
 25 7, 14, 21, and 28 days post occlusion.

Methods

Animals, Housing and Diet: Adult, male Sprague-Dawley rats were obtained 7-10 days prior to surgery from Charles River Laboratories (Kingston, NY). Animals were assigned sequential identification numbers using permanent marker on the tail. Animals were housed in rooms provided
5 with filtered air at a temperature of $21 \pm 2^\circ \text{C}$ and $50\% \pm 20\%$ relative humidity. The room was on an automatic timer for a light/dark cycle of 12 hours on and 12 hours off with no twilight. Bed-O-Cobs® was used for bedding and animals were fed with standard Purina 5001 chow. Food and water was provided ad libitum. Animals were handled for behavioral
10 assessment for seven (7) days prior to surgery for acclimation purposes. At the end of the handling period, rats were randomized and assigned to different groups.

Middle Cerebral Artery Occlusion (MCA-o), modified Tamura Model:
Focal cerebral infarcts were made by permanent occlusion of the proximal
15 right middle cerebral artery (MCA) using a modification of the method of Tamura et al. (Tamura A, Graham DI, McCulloch J, Teasdale GM. (1981a) "Focal cerebral ischemia in the rat. 1. Description of technique and early neuropathological consequences following middle cerebral artery occlusion". J Cereb Blood Flow Metab 1: 53–60). Male Sprague-Dawley rats (300-400 g at
20 the time of surgery) were anesthetized with 2~3% halothane in the mixture of N₂O : O₂ (2:1), and were maintained with 1~1.5 % halothane in the mixture of N₂O : O₂ (2:1). The temporalis muscle was bisected and reflected through an incision made midway between the eye and the eardrum canal. The proximal MCA was exposed through a subtemporal craniectomy without removing the
25 zygomatic arch and without transecting the facial nerve. The artery was then occluded by microbipolar coagulation from just proximal to the olfactory tract to the inferior cerebral vein, and was transected. Body temperature was maintained at $37.5^\circ\text{C} \pm 0.5^\circ\text{C}$ throughout the entire procedure. Cefazolin (40 mg/kg; BaxterHealthcare, Deerfield, Ill) was given i.p. one day before MCA-o
30 and just after MCA-o to prevent infections.

Compound Preparation and Dosing: Compound powder was stored at room temperature (20-25° C). The compound solutions were made fresh each day before the first subcutaneous injection. Animals received 2 ml/kg of solution. The vehicle was saline.

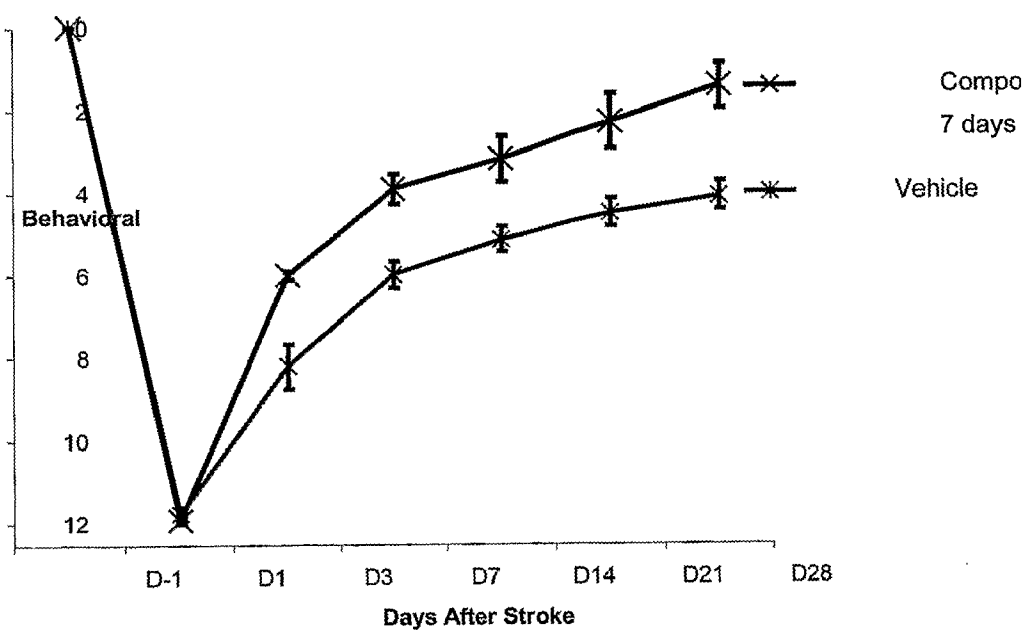
- 5 Randomization and Blinding: Five animals were operated on per day. The investigator doing the surgery and behavioral assessments was blinded to treatment assignment of each animal until all of the data were collected and analyzed.

- 10 Behavioral Tests: Functional activities were evaluated using limb placing and body swing behavioral tests. These tests were performed one day before surgery (baseline), one day after surgery and at three (3), seven (7), fourteen (14), twenty-one (21) and twenty-eight (28) days after MCA-O.

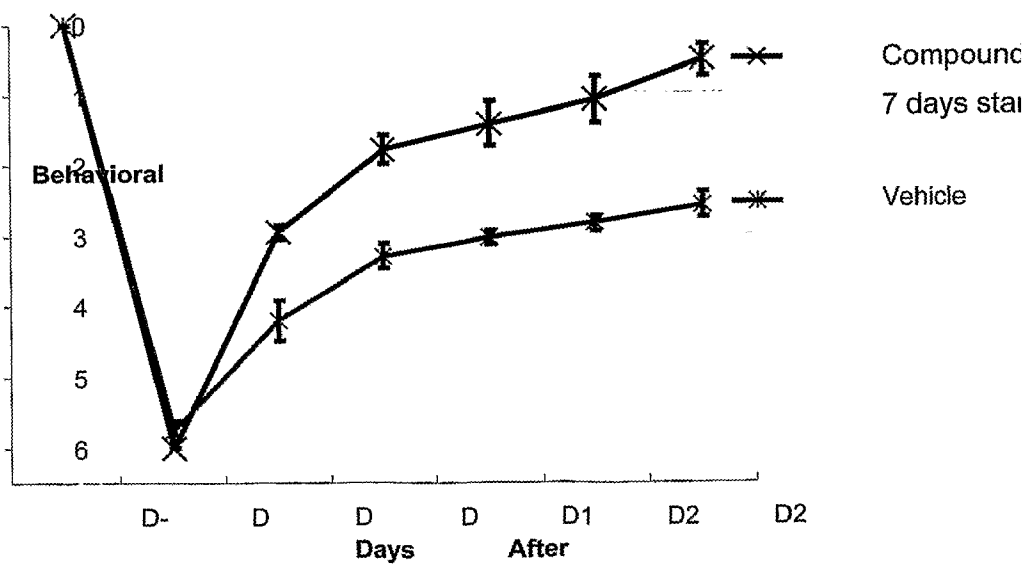
- 15 Limb Placing: Limb placing tests were divided into both forelimb and hindlimb tests. For the forelimbplacing test, the examiner held the rat close to a tabletop and scored the rat's ability to place the forelimb on the tabletop in response to whisker, visual, tactile, or proprioceptive stimulation. Similarly, for the hindlimb placing test, the examiner assessed the rat's ability to place the hindlimb on the tabletop in response to tactile and proprioceptive stimulation. Separate sub-scores were obtained for each mode of sensory input (halfpoint designations possible), and added to give total scores (for the forelimb placing test: 0 = normal, 12 = maximally impaired; for the hindlimb placing test: 0 = normal; 6 = maximally impaired).
- 20

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Forelimb Placing Test



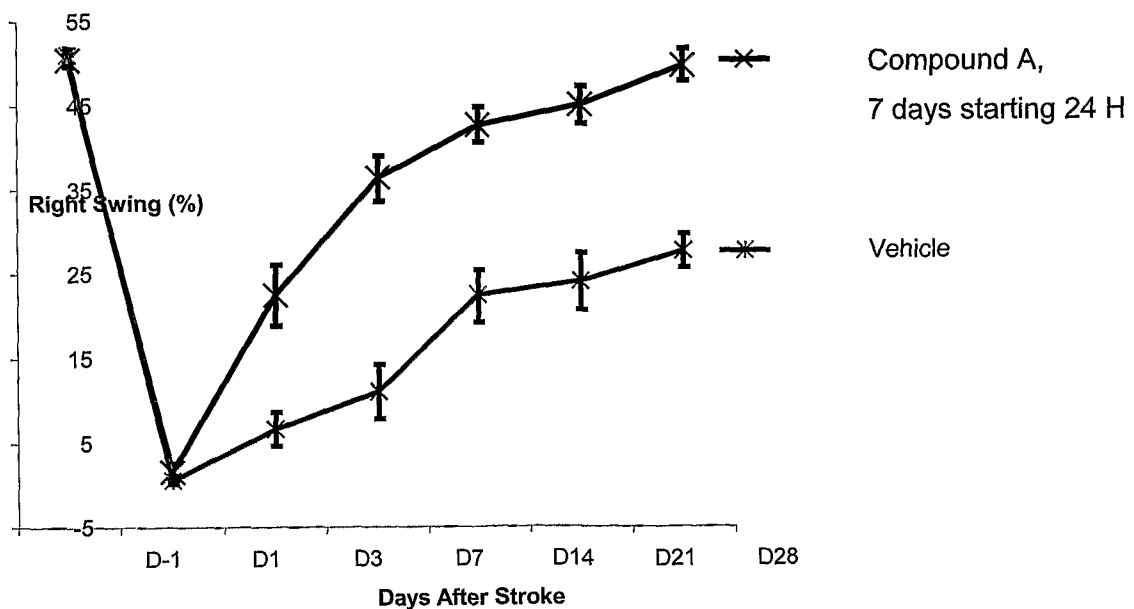
Hindlimb Placing Test



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Body Swing Test: The rat was held approximately one inch from the base of its tail. It was then elevated to an inch above a surface of a table. The rat was held in the vertical axis, defined as no more than 10° to either the left or the right side. A swing was recorded whenever the rat moved its head out of the vertical axis to either side. The rat must return to the vertical position for the next swing to be counted. Thirty (30) total swings were counted. A normal rat typically has an equal number of swings to either side. Following focal ischemia, the rat tends to swing to the contralateral (left) side.

Body Swing Test



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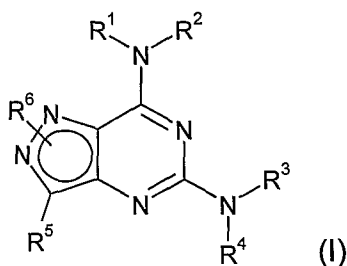
On Day 1 after surgery, behavior was tested in the morning, and drugs administered in the afternoon. For all other days, drugs were administered in the morning, and behavior was tested in the afternoon. All data are expressed as mean $\pm$ S.E.M.

5 The above results show that in all tests – Forelimb placing test, Hindlimb placing test, and Body swing test – compound A performed significantly better than a vehicle.

10 The previous examples are intended only for illustrative purposes, and do not limit the scope of the invention, which is defined by the appended claims.

WE CLAIM:

1. A method for promoting functional recovery in a mammal, comprising administering to the mammal a compound of formula (I)



5 wherein

R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

R^3 and R^4 are each independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl or C_3 - C_{10} cycloalkyl, each of which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups, or hydrogen;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

15 R^5 is selected from $-Y-CO_2R^{15}$ and $-Y-R^{16}$;

R^6 , which may be attached at N^1 or N^2 , is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl, each of which is optionally substituted by C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or a cyclic group selected from R^J , R^K , R^L and R^M , or R^6 is R^N , C_3 - C_7 cycloalkyl or C_3 - C_7 halocycloalkyl, each of which is optionally substituted by C_1 - C_6 alkoxy or C_1 - C_6 haloalkoxy, or R^6 is hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN ;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , C_3 - C_6

cycloalkyl, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} ,
 5 $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} ,
 $CONR^{12}R^{13}$, CN , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are
 optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6
 10 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{15} is hydrogen or C_1 - C_6 alkyl optionally substituted with one or more
 groups selected from phenyl, halo, OH, C_1 - C_6 alkyloxy, NH_2 , $NH(C_1$ - C_6 alkyl)
 and $N(C_1$ - C_6 alkyl) $_2$;

15 R^{16} is a carboxylic acid isostere selected from tetrazol-5-yl, 5-
 trifluoromethyl-1,2,4-triazol-3-yl, 5-(methylsulfonyl)-1,2,4-triazol-3-yl, 2,5-
 dihydro-5-oxo-1,2,4-oxadiazol-3-yl, $-SO_2NHR^{17}$ and $-CONHR^{18}$;

R^{17} is selected from C_1 - C_6 alkyl, phenyl, $-CO-(C_1$ - C_6 alkyl) and $-$
 CO-phenyl;

20 R^{18} is selected from $-SO_2-(C_1$ - C_6 alkyl) and $-SO_2$ -phenyl;

R^A and R^J are each independently a C_3 - C_{10} cycloalkyl or C_3 - C_{10}
 cycloalkenyl group, each of which may be either monocyclic or, when there
 are an appropriate number of ring atoms, polycyclic and which may be fused
 to either

25 (a) a monocyclic aromatic ring selected from a benzene ring and a
 5- or 6-membered heteroaromatic ring containing up to three heteroatoms
 selected from nitrogen, oxygen and sulphur, or

(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to
 three heteroatoms selected from nitrogen, oxygen and sulphur;

30 R^B and R^K are each independently a phenyl or naphthyl group, each of
 which may be fused to

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- (a) a C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl ring,
(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or
(c) a 5- or 6-membered heteroaromatic ring containing up to three
5 heteroatoms selected from nitrogen, oxygen and sulphur;

R^C, R^L and R^N are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated or partly unsaturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which
10 ring may be fused to a C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl group or a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^D and R^M are each independently a 5- or 6-membered heteroaromatic
15 ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur, which ring may further be fused to

- (a) a second 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;
(b) C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl ring;
20 (c) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur; or
(d) a benzene ring;

R^E, R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system
25 containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond, -CH₂-O-CH₂-, C₁-C₆ alkylenyl or C₃-C₇
30 cycloalkylenyl;

a tautomer thereof or a pharmaceutically acceptable salt of said compound or tautomer.

2. A method according to claim 1 wherein R^1 is R^D , which is optionally substituted with one or more R^7 groups.

5 3. A method according to claim 2 wherein R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

4. A method according to claim 3 wherein R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen
10 and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms.

5. A method according to claim 4 wherein R^D is furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

15 6. A method according to claim 5 wherein R^D is pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

7. A method according to claim 1 wherein R^2 is hydrogen or methyl.

20 8. A method according to claim 7 wherein R^2 is hydrogen.

9. A method according to claim 1 wherein R^3 is hydrogen, C_1 - C_6 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic or, when there are an appropriate number of ring atoms,
25 polycyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

10. A method according to claim 9 wherein R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which
30 is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of

which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

11. A method according to claim 10 wherein R^3 is C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups and wherein R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.

12. A method according to claim 10 wherein R^3 is hydrogen or C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^3 is azetidiny, pyrrolidiny or piperidiny, each of which is optionally substituted with one or more R^9 groups, wherein

R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, $NMeCO_2^tBu$, CO_2H , $CONHMe$, pyrrolidiny, piperidiny, morpholiny or pyrazolyl, the last four of which are optionally substituted with one or more R^9 groups and wherein

R^9 is methyl or CO_2^tBu .

13. A method according to claim 1 wherein R^4 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl.

14. A method according to claim 13 wherein R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl.

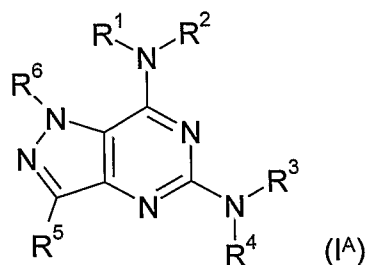
15. A method according to claim 14 wherein R^4 is hydrogen, methyl or ethyl.

16. A method according to claim 1 wherein R^5 is $-Y-R^{16}$.

17. A method according to claim 16 wherein R^{16} is $-CONHR^{18}$, tetrazol-5-yl or 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl and Y is a covalent bond or a methylene group.

18. A method according to claim 1 wherein the compound of formula I corresponds in structure to formula (I^A)

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19. A method according to claim 1 wherein the compound of formula I is selected from:

- methyl 5-((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
- 5 methyl 1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylanino)-7-(6-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
- ethyl 1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
- 10 2-(dimethylamino)ethyl 5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate,
- 1-(2-ethoxyethyl)-5-(*N*-methyl-*N*-propylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 5-(*N*-isopropyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1-(2-propoxy-ethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 15 7-(4,6-dimethylpyridin-2-ylamino)-1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methyl-amino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 5-(*N*-cyclobutyl-*N*-methylanino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 20 1-(2-ethoxyethyl)-5-isopropylanino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylanino)-7-(2-methoxypyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
- 3-[1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylanino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]-2*H*-1,2,4-oxadiazol-5-one,
- 25

- 3-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]-2*H*-1,2,4-oxadiazol-5-one,
1-(2-ethoxyethyl)-7-(4-fluoro-3-methylphenylamino)-5-(*N*-isopropyl-*N*-methylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
5 1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-fluoro-3-methylphenylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
7-(3,4-dimethylphenylamino)-1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-(cyclopropylmethoxy)ethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
10 1-(2-(cyclopropylmethoxy)ethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
15 1-(2-isopropoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid,
N-[1-(2-ethoxyethyl)-5-(*N*-isopropyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide,
N-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide,
20 *N*-[5-(Ethyl-methyl-amino)-1-[2-(3-fluoro-propoxy)-ethyl]-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide
N-[1-[2-(3-Fluoro-propoxy)-ethyl]-5-(isopropyl-methyl-amino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide
25 *N*-[5-Diethylamino-1-[2-(3-fluoro-propoxy)-ethyl]-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide
N-[5-Diethylamino-1-[2-(2,2-difluoro-ethoxy)-ethyl]-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide
30

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N-[1-[2-(2,2-Difluoro-ethoxy)-ethyl]-5-(ethyl-methyl-amino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide, and

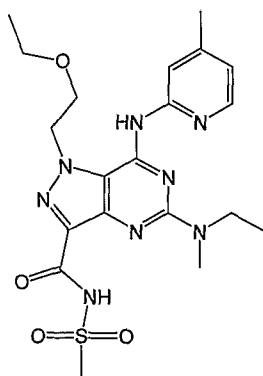
N-[1-[2-(2,2-Difluoro-ethoxy)-ethyl]-5-(isopropyl-methyl-amino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]-methanesulfonamide,

or a tautomer thereof or a pharmaceutically acceptable salt of said compound or tautomer.

20. A method according to claim 1 wherein the compound of formula 10 is

N-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide or a tautomer thereof or a pharmaceutically acceptable salt of said compound or tautomer.

21. A method for promoting functional recovery in a mammal, comprising administering to the mammal a compound of Tautomer (1) of *N*-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]methanesulfonamide,



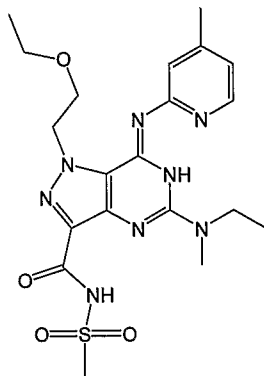
Tautomer (1)

or a pharmaceutically acceptable salt of said tautomer.

22. A method for promoting functional recovery in a mammal, comprising administering to the mammal a compound of Tautomer (2) of *N*-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-

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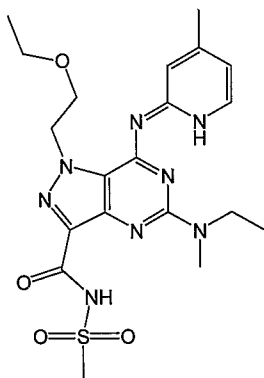
pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide,



Tautomer (2)

or a pharmaceutically acceptable salt of said tautomer.

23. A method for promoting functional recovery in a mammal,
 5 comprising administering to the mammal a compound of Tautomer (3) of N-[1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide,



Tautomer (3)

or a pharmaceutically acceptable salt of said tautomer.

- 10 24. A method according to claim 20, 21, 22, or 23 wherein the functional recovery is functional recovery following traumatic brain injury, craniocerebral trauma, stroke, spinal cord trauma, cerebral ischemia, multi-infarct dementia, post-CABG dementia, subdural hematoma, or subarachnoid hemorrhage.

25. A method according to claim 1 wherein the functional recovery is functional recovery following traumatic brain injury, craniocerebral trauma, stroke, spinal cord trauma, cerebral ischemia, multi-infarct dementia, post-CABG dementia, subdural hematoma, or subarachnoid hemorrhage.