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(54) Title: VITRONECTIN RECEPTOR ANTAGONISTS USEFUL FOR THE TREATMENT OF STROKES

(57) Abstract: This invention relates to the use of a vitronectin receptor antagonist to treat stroke.

VITRONECTIN RECEPTOR ANTAGONISTS USEFUL FOR THE TREATMENT OF STROKES

Field of the Invention

This invention relates to the use of antagonists of the vitronectin receptor to treat stroke.

Background of the Invention

Integrins are a superfamily of cell adhesion receptors that couple intracellular cytoskeletal elements with extracellular matrix molecules. These cell surface adhesion receptors include $\alpha_V\beta_3$ (the vitronectin receptor). The vitronectin receptor $\alpha_V\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells mediates the adhesion of osteoclasts to the bone matrix, a key step in the bone resorption process. Ross, et al., *J. Biol. Chem.*, **1987**, *262*, 7703. The $\alpha_V\beta_3$ receptor expressed on human aortic smooth muscle cells mediates their migration into neointima, a process which can lead to restenosis after percutaneous coronary angioplasty. Brown, et al., *Cardiovascular Res.*, **1994**, *28*, 1815. Additionally, Okada, et al., *Am. J. Pathol.*, **1996**, *149(1)*, 37 suggest that $\alpha_V\beta_3$ plays a role in vascular integrity and remodeling following focal ischemia within an infarcted area. In a non-human primate model of transient fore-brain ischemia, the $\alpha_V\beta_3$ receptor upregulated early in the ischemic event.

Surprisingly, it has been found that vitronectin receptor antagonists would be useful in treating stroke and the post-traumatic injury associated with stroke.

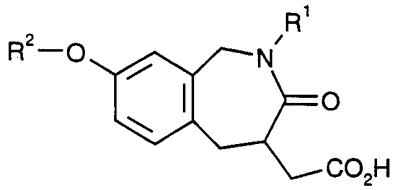
Summary of the Invention

The present invention provides a new method of treatment of stroke in a mammal, in particular a man, which comprises administering to a subject in need thereof an effective amount of a vitronectin receptor antagonist.

Detailed Description of the Invention

The present invention is a therapeutic method for treating stroke and a method for protecting the central nervous system from traumatic and post-traumatic injury associated with stroke, e.g., prevention of neurotrauma, and the reduction of morbidity resulting from the sequelae of stroke. The method utilizes a class of antagonists which have been prepared and evaluated as effective vitronectin receptor antagonists. Examples of suitable vitronectin receptor antagonists include, but are not limited to, the following:

Benzazepine ethers of the formula (I), which are described in PCT Application No. PCT/US97/18001, filed October 1, 1997, published as WO 98/14192 on April 9, 1998:



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -NO_2, or tetrazolyl;

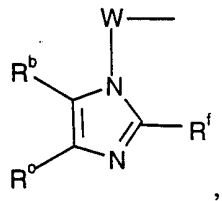
each R^8 independently is -OR', -NR'R", -NR'SO_2R', -NR'OR', or -$OCR'_2CO(O)R'$;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -$NR'R^{11}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is



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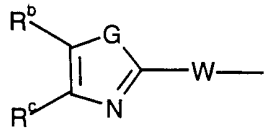

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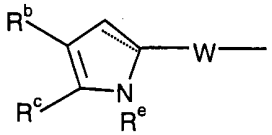

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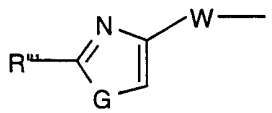

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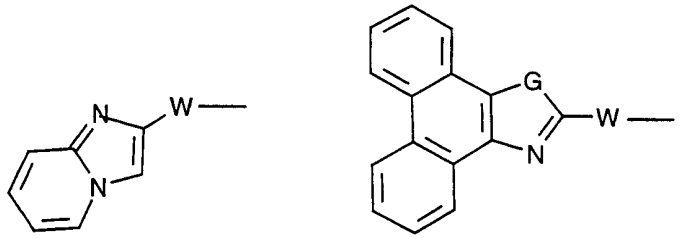
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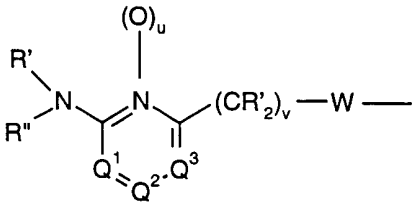
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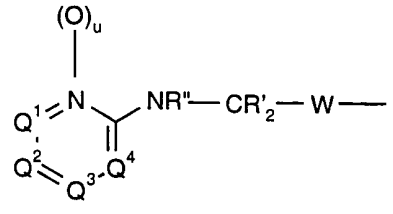
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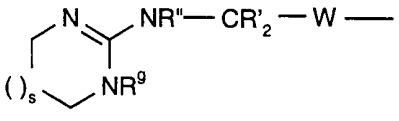

;

W is $-(CHR^g)_a-U-(CHR^g)_b-$;

U is absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, $CONR^i$, NR^iCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, NR^gNR^g, $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl, or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;

R^f is H, C_{1-6}alkyl or Ar-C_{0-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, or $(CH_2)_kCO_2R^g$;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, -OR^g, -SR^g, -CN, -NR^gR^k, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$, or C_{1-6}alkyl optionally substituted by halo, -OR^g, -SR^g, -CN, -NR^gR", -NO_2, -CF_3, R'$S(O)_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

Preferred formula (I) compounds used in the method of this invention are (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid and (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, or pharmaceutically acceptable salts thereof.

Additional examples of vitronectin receptor antagonists used in the method of this invention include those antagonists described in the following: PCT Application No. PCT/US95/08306, filed June 29, 1995, published as WO 96/00730 on January 11, 1996; PCT Application No. PCT/US95/08146, filed June 29, 1995, published as WO 96/00574 on January 11, 1996; PCT Application No. PCT/US96/11108, filed June 28, 1996, published as WO 97/01540 on January 16, 1997; PCT Application No. PCT/US96/20748, filed December 20, 1996, published as WO 97/24119 on July 10, 1997; PCT Application No. PCT/US96/20744, filed December 20, 1996, published as WO 97/24122 on July 10, 1997; PCT Application No. PCT/US96/20327, filed December 20, 1996, published as WO 97/24124 on July 10, 1997; PCT Application No. PCT/US98/00490, filed January 8, 1998, published as WO 98/30542 on July 16, 1998; PCT Application No. PCT/US98/19466, filed September 18, 1998, published as WO 99/15508 on April 1, 1999; and PCT Application No. PCT/US99/28662, filed December 3, 1999, published as WO

00/33838 on June 15, 2000. The preferred compound in PCT Application WO 00/33838 is (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid. This compound is useful in the method of this invention.

The above list of vitronectin receptor antagonists for use in the method of the present invention were taken from published patent applications. Reference should be made to each patent application for its full disclosure, including the methods of preparing the disclosed compounds, the entire disclosure of each patent application being incorporated herein by reference.

In accordance with the present invention, it has been found that the administration of a vitronectin receptor antagonist to a stroke patient minimizes the worsening of the infarction and aids in the prevention of a second stoke.

During ischemic organ trauma, as in stroke, a high proportion of ischemic organ cells become irreversibly damaged and necrotic, the extent of injury being dependent upon the length of time that the trauma, e.g. the arterial occlusion, persists. Thus, it is an object of the instant invention to protect the central nervous system neurons from such damage and necrosis during occlusion occurring in stroke and post-traumatic reperfusion.

In the therapeutic use for the treatment of stroke, the vitronectin receptor antagonist is incorporated into standard pharmaceutical compositions. It can be administered orally, parenterally, rectally, topically or transdermally.

Pharmaceutical compositions of the vitronectin receptor antagonist may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, the vitronectin receptor antagonist may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic

acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to be effective. The pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An intravenous infusion of the peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

No unacceptable toxicological effects are expected when eprosartan is administered in accordance with the present invention.

Materials and Methods

Focal brain ischemia: Permanent or temporary cerebral focal ischemia or sham surgery was carried out under stereotaxic control in male spontaneously hypertensive rats (SHR) or in normotensive rat strain (Wistar-Kyoto), at 18 weeks of age weighing 250-330 grams, by permanent or temporary MCAO as described in

detail previously (Barone FC, Price WJ, White RF, Willette RN, Feuerstein GZ (1992) Genetic hypertension and increased susceptibility to cerebral ischemia. Neurosc Biobehav Rev 16:219-233; Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Griswold DE, Sarau HM (1992) Reperfusion increases neutrophil and LTB_4 receptor binding in focal ischemia. Stroke 23:1337-1348; Barone FC, Hillegass LM, Tzimas MN, Schmidt DB, Foley JJ, White RF, Price WJ, Feuerstein GZ, Clark RK, Griswold DE and Sarau HM (1995) Time-related changes in myeloperoxidase activity and leukotriene B_4 receptor binding reflect leukocyte influx in cerebral focal stroke. Mol Chem Neuropathol 24:13-30; Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG, Feuerstein GZ (1997) Tumor necrosis factor α: A mediator of focal ischemic brain injury. Stroke 28:1233-1244). These models are similar to those established and utilized by others (Brint S, Jacewicz M, Kiessling M, Tanable J, Pulsinelli W (1988) Focal brain ischemia in the rat: Methods for reproducible neocortical infarction using tandem occlusion of the distal middle cerebral artery and ipsilateral common carotid arteries. J Cereb Blood Flow Metabol 8:474-485; Buchan AM, Xue D, Slivka A (1992) A new model of temporary focal neocortical ischemia in the rat. Stroke 23: 273-279; Duverger D, MacKenzie T (1988) The quantification of cerebral infarction following focal ischemia in the rat: Influence of strain, arterial pressure, blood glucose concentration, age. J Cereb Blood Flow Metab 8:449-461) and have been extensively characterized over time, indicating extended time course evaluations, for consistency of ischemic cortical blood flow effects and infarction (Barone FC, Price WJ, White RF, Willette RN, Feuerstein GZ (1992) Genetic hypertension and increased susceptibility to cerebral ischemia. Neurosc Biobehav Rev 16:219-233; Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Griswold DE, Sarau HM (1992) Reperfusion increases neutrophil and LTB_4 receptor binding in focal ischemia. Stroke 23:1337-1348), neurological deficits (Barone FC, Clark RK, Price WJ, White RF, Storer BL, Feuerstein GZ, Ohlstein EH (1993) Neuron specific enolase increases in cerebral and systemic circulation following focal ischemia. Brain Res 623:77-82), increased cytokine expression and influence on tissue injury (Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG, Feuerstein GZ (1997) Tumor necrosis factor α: A mediator of focal ischemic brain injury. Stroke 28:1233-1244; Wang XK, Barone FC, Aiyar NV, Feuerstein GZ (1997) Increased interleukin-1 receptor and interleukin-1 receptor antagonist gene expression after focal stroke. Stroke 28:155-162), cellular infiltration, inflammation, tissue changes and resolution of injury (Clark RK, Lee EV, Fish CJ, White RF, Price WJ, Jonak

ZL, Feuerstein GZ and Barone FC (1993) Progression of cerebral changes following middle cerebral artery occlusion in the rat: A quantitative planimetric, histologic and immunohistochemical study. Brain Res Bull 31: 565-572; Clark RK, Lee EV, White RF, Jonak ZL, Feuerstein GZ and Barone FC (1994) Reperfusion following focal stroke hastens inflammation and resolution of ischemic injured tissue. Brain Res Bull 35:387-391; Barone FC, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Sarau HM, Clark RK, Griswold DE (1991) Polymorphonuclear leukocyte infiltration into cerebral focal ischemic tissue: Myeloperoxidase activity assay and histologic verification. J Neurosci Res 29:336-348; Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Griswold DE, Sarau HM (1992b) Reperfusion increases neutrophil and LTB_4 receptor binding in focal ischemia. Stroke 23:1337-1348; Barone FC, Hillegass LM, Tzimas MN, Schmidt DB, Foley JJ, White RF, Price WJ, Feuerstein GZ, Clark RK, Griswold DE and Sarau HM (1995) Time-related changes in myeloperoxidase activity and leukotriene B_4 receptor binding reflect leukocyte influx in cerebral focal stroke. Mol Chem Neuropathol 24:13-30) and influence of temperature on injury (Barone FC, Feuerstein GZ, White RF (1997) Reduced brain temperature during transient focal ischemia provides complete neuroprotection. Neurosci Biobehav Rev 21:31-44). Complete tissue injury/necrosis is observed by 24 h of permanent MCAO or within 24 h of reperfusion in these models (Clark RK, Lee EV, Fish CJ, White RF, Price WJ, Jonak ZL, Feuerstein GZ and Barone FC (1993) Progression of cerebral changes following middle cerebral artery occlusion in the rat: A quantitative planimetric, histologic and immunohistochemical study. Brain Res Bull 31: 565-572; Clark RK, Lee EV, White RF, Jonak ZL, Feuerstein GZ and Barone FC (1994) Reperfusion following focal stroke hastens inflammation and resolution of ischemic injured tissue. Brain Res Bull 35:387-391). Briefly, for permanent MCAO, the middle cerebral artery was permanently occluded and cut dorsal to the lateral olfactory tract at the level of the inferior cerebral vein using electrocoagulation (Force 2 Electrosurgical Generator, Valley Lab Inc.). For temporary MCAO with reperfusion, the MCA was lifted from the brain surface to occlude blood flow for 160 min and then reperfused as described in detail previously (Barone FC, Price WJ, White RF, Willette RN, Feuerstein GZ (1992) Genetic hypertension and increased susceptibility to cerebral ischemia. Neurosc Biobehav Rev 16:219-233; Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Griswold DE, Sarau HM (1992) Reperfusion increases neutrophil and LTB_4 receptor binding in focal ischemia. Stroke 23:1337-1348; Barone FC, Hillegass LM, Tzimas MN, Schmidt DB, Foley JJ, White RF, Price WJ, Feuerstein GZ, Clark

RK, Griswold DE and Sarau HM (1995) Time-related changes in myeloperoxidase activity and leukotriene B_4 receptor binding reflect leukocyte influx in cerebral focal stroke. Mol Chem Neuropathol 24:13-30; Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG, Feuerstein GZ (1997) Tumor necrosis factor α: A mediator of focal ischemic brain injury. Stroke 28:1233-1244). Blood flow determinations have demonstrated the validity of these techniques, i.e., flow is permanently decreased less than 25% of baseline following permanent MCAO, and recovers to 100% of blood flow following reperfusion of the temporary MCAO (Barone FC, Price WJ, White RF, Willette RN, Feuerstein GZ (1992) Genetic hypertension and increased susceptibility to cerebral ischemia. Neurosc Biobehav Rev 16:219-233). SHR were selected as the focus of study in the present experiments because of their consistent response to permanent or transient focal ischemic injury (i.e., consistent infarctions with low variability) (Barone FC, Price WJ, White RF, Willette RN, Feuerstein GZ (1992) Genetic hypertension and increased susceptibility to cerebral ischemia. Neurosc Biobehav Rev 16:219-233; Duverger D, MacKenzie T (1988) The quantification of cerebral infarction following focal ischemia in the rat: Influence of strain, arterial pressure, blood glucose concentration, age. J Cereb Blood Flow Metab 8:449-461; Ginsberg DM, Busto R (1989) Rodent models of cerebral ischemia. Stroke 20:1627-1642). Body temperature was maintained at 37 °C using a heating pad during all surgical procedures and continued to be regulated at 37 °C after head closure (i.e., during recovery of anesthesia) for several hours until normal motor activity was resumed by individual animals. In sham-operated rats the dura was opened over the MCA but the artery was not occluded. Rats then were overdosed with pentobarbital and forebrains were removed at 1, 3, 6 and 12 h, and 1, 2, 5, 10 and 15 days following permanent MCAO or after reperfusion following temporary MCAO, and at 12 h and 5 days following sham surgery. The ischemic cortex (i.e., the cortex ipsilateral to surgery) was dissected from the ipsilateral hemisphere; the contralateral (control) cortex was dissected from the non-ischemic contralateral hemisphere from the same rat (Barone FC, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Sarau HM, Clark RK, Griswold DE (1991) Polymorphonuclear leukocyte infiltration into cerebral focal ischemic tissue: Myeloperoxidase activity assay and histologic verification. J Neurosci Res 29:336-348; Barone FC, Schmidt DB, Hillegass LM, Price WJ, White RF, Feuerstein GZ, Clark RK, Griswold DE, Sarau HM (1992) Reperfusion increases neutrophil and LTB_4 receptor binding in focal ischemia. Stroke 23:1337-1348; Barone FC, Hillegass LM, Tzimas MN, Schmidt DB, Foley JJ, White RF, Price WJ, Feuerstein GZ, Clark RK, Griswold DE and Sarau HM

(1995) Time-related changes in myeloperoxidase activity and leukotriene B_4 receptor binding reflect leukocyte influx in cerebral focal stroke. Mol Chem Neuropathol 24:13-30; Wang XK, Barone FC, Aiyar NV, Feuerstein GZ (1997) Increased interleukin-1 receptor and interleukin-1 receptor antagonist gene expression after focal stroke. Stroke 28:155-162). The cortical samples were immediately frozen in liquid nitrogen and stored at -80 °C.

Northern hybridization analysis: For RNA preparation, cortical samples were homogenized in an acid guanidinium thiocyanate solution and extracted with phenol and chloroform as described previously (Chomczynski P, Sacchi N (1987) Single-step method of RNA isolation by acid guanidinum thiocyanate-phenol-chloroform extraction. Anal Biochem 162:156-159; Wang XK, Siren A-L, Liu Y, Yue T-L, Barone FC, Feuerstein GZ (1994) Upregulation of intercellular adhesion molecule 1 (ICAM-1) on brain microvascular endothelial cells in rat ischemic cortex. Mol Brain Res 26:61-68). RNA samples (40 µg/lane) were electrophoresed through formaldehyde-agarose slab gels and transferred to GeneScreen Plus membranes (DuPont-New England Nuclear). For Northern blot analysis, an OPN or ribosomal protein L32 cDNA was prepared as described previously (Wang XK, Louden C, Ohlstein EH, Stadel JM, Gu JL, Yue TL (1996) Osteopontin expression in platelet-derived growth factor-stimulated vascular smooth muscle cells and carotid artery after balloon angioplasty. Aterioscler Thromb Vasc Biol 16:1365-1372), and was uniformly labeled with [α-^{32}P]dATP (3000 Ci/mmol, Amersham Corp) using a random-priming DNA labeling kit (Boehringer Mannheim). Hybridization of each probe was carried out overnight with $1x10^6$ cpm/ml of probe at 42 °C in 5 x SSPE (750 mM NaCl, 50 mM NaH_2PO_4, pH7.6, 5 mM EDTA), 50% formamide, 5 x Denhardt's solution, 2% SDS, 100 µg/ml polyA and 200 µg/ml boiled salmon sperm DNA. The membranes were washed in 2 x SSPE, 2% SDS at 65 °C for 1-2 hr with a change every 30 min, then autoradiographed at -70 °C with a Cronex Lightning-Plus intensifying screen for various times depending upon the signal intensity. The relative band intensities were measured using a PhosphorImager with an ImageQuant software package (Molecular Dynamics). A probe was stripped from the membranes in 10 mM Tris, pH 7.5, 1 mM EDTA, pH 8.0, 1% SDS for 20 min at 95 °C and then washed in 2 x SSPE for 10 min prior to re-hybridization with the other probe. The expression of rpL32 gene is relatively constant in the present experimental conditions (Wang XK, Siren A-L, Liu Y, Yue T-L, Barone FC, Feuerstein GZ (1994) Upregulation of intercellular adhesion molecule 1 (ICAM-1) on brain microvascular endothelial cells in rat ischemic cortex. Mol Brain Res 26:61-68; Wang XK, Yue T-L, Barone FR, White RF, Feuerstein GZ (1994)

Concomitant cortical expression of TNF-α and IL-1β mRNAs follows early response gene expression in transient focal ischemia. Mol Chem Neuropathol 23:103-114) and therefore was used to normalize the differences of the samples loaded in each lane.

In situ hybridization: Tissue preparation, *in vitro* transcription, and combined *in situ* hybridization and immunohistochemistry was carried out as reported previously (Ellison JA, Scully SA, de Vellis J (1996) Evidence for neuronal regulation of oligodendrocyte development: cellular localization of platelet-derived growth factor a receptor and A-chain mRNA during rat cerebral cortex development. J Neurosci Res 45:28-39) with slight modifications to the *in situ* hybridization protocol as indicated. Tissue sections (12 μm) were incubated with the ED1 antibody (Biosource International) overnight at 4 °C. Detection of the antibody was performed using the Vector Labs ABC kit according to the manufacturer's instructions using diaminobenzidine as the substrate. Immediately after antibody detection, tissue was deproteinated in 0.2 M HCl then acetylated with 0.1 M triethanolamine (pH 8) with 0.25% acetic anhydride. Antisense or sense [^{33}P]UTP labeled OPN probes (1x10^6 cpm/ml) were applied to tissue and hybridized overnight at 60 °C. Posthybridization washes were modified as follows: 4 X SSC twice for 10 min each at 50 °C; 20 μg/ml RNase 30 min at 37 °C; 5 min each 2 X SSC, 1 X SSC, 0.5 X SSC at room temperature; 0.1 X SSC 20 min at 55 °C; 0.1 X SSC 5 min at room temperature. Slides were dehydrated and dried then exposed to Hyperfilm βmax (Amersham) overnight. For emulsion autoradiography slides were dipped in NTB2 emulsion (Kodak) and exposed for 7 days at 4 °C.

Immunohistochemistry: For immunohistochemical studies, rats were sacrificed at 6, 12 and 24 h, and 5, 10 and 15 days after permanent MCAO. Following whole body perfusion with 10% phosphate buffered formalin the brain from three rats (n=3) at each time point was excised and stored in formalin for 24 h after which the samples were transferred to 70% ethanol and then subjected to standard histological processing using a Vacuum Infiltration Processor (Miles). After paraffin embedding, 5-μm sections were cut and stained with hematoxylin and eosin, and evaluated microscopically. Additional sections were placed on Capillary Gap Plus Microscope Slides (BioTek) for immunohistochemical evaluation of OPN, ED-1 (monocyte/macrophage marker), Glial Fribillary Acidic Protein (GFAP; marker for activated glia) and S-100 (neurofilament marker) expression.

Immunohistochemistry was carried out as described previously (Wang XK, Louden C, Ohlstein EH, Stadel JM, Gu JL, Yue TL (1996) Osteopontin expression in platelet-derived growth factor-stimulated vascular smooth muscle cells and carotid

artery after balloon angioplasty. Aterioscler Thromb Vasc Biol 16:1365-1372) using mouse anti-rat OPN antibody, MPIIIB10 (Developmental Studies Hybridoma Bank, University of Iowa, Iowa City, IA; at 1:50 dilution), monoclonal anti-ED1 (Harlan Bioproducts for Science; at 1:100 dilution), rabbit anti-cow GFAP (DAKO; at a dilution of 1:750 or 1:20,000) and rabbit anti-cow S-100 (DAKO; at 1:20,000 dilution), respectively.

Cell culture and migration assay: Rat C6 glial cells (ATCC CCL107) were obtained from American Type Cultured Collection (ATCC) and cultured in Dulbecco's modified Eagle's medium (DMEM) (GIBCO BRL) supplemented with 5% fetal bovine serum. Normal human astrocytes were purchased from Clonetics and cultured in an astrocyte basal medium (Clonetics) containing 5% fetal bovine serum, 20 ng/ml hEGF, 25 microg/ml insulin, 25 ng/ml progesterone, 50 microg/ml transferrin, 50 microg/ml gentamicin and 50 ng/ml amphotericin-B. The human astrocytes were maintained and subcultured according to the manufacturer's specification, and applied for the cell migration assays prior to the passage 3.

Cell migration assays were performed in a Transwell cell culture chamber using a polycarbonate membrane with 8 microM pores (Costar) as reported previously (Hidaka YT, Eda T, Yonemoto M, Kamei T (1992) Inhibition of cultured vascular smooth muscle cell migration by simvastatin (MK-7333). Atherosclerosis 95:87-94). The lower surface of the membrane was pre-coated with different concentration of recombinant rat OPN (Yue TL, McKenna PJ, Ohlstein EH, Farach-Carson MC, Butler WT, Johanson K, McDevitt P, Feuerstein GZ, Stadel JM (1994) Osteopontin-stimulated vascular smooth muscle cell migration is mediated by β3 integrin. Exp Cell Res 214:459-464). C6 cells were suspended in DMEM and human astrocytes were resuspended in astrocyte basal medium supplemented with 0.2% bovine serum albumin at a concentration of 3×10^6 and 2×10^5 cells per milliliter, respectively. As a standard assay, 0.2 ml of cell suspension was placed in the upper compartment of the chamber, and the lower compartment contained 0.6 ml of DMEM or astrocyte basal medium supplemented with 0.2% bovine albumin prior to use. Incubation was carried out at 37 °C in 5% CO_2 for 24 h. After incubation, nonmigrated cells on the upper surface were scraped gently, and the filters were fixed in methanol and stained 10% Giemsa stain. The number of cells migrated to the lower surface of the filters was either measured by optical density at 640 nm (C6 cells) or countered four high power fields (x100) per filter (Hidaka YT, Eda T, Yonemoto M, Kamei T (1992) Inhibition of cultured vascular smooth muscle cell migration by simvastatin (MK-7333). Atherosclerosis 95:87-94; Yue TL, McKenna PJ, Ohlstein EH, Farach-Carson MC, Butler WT, Johanson K, McDevitt P,

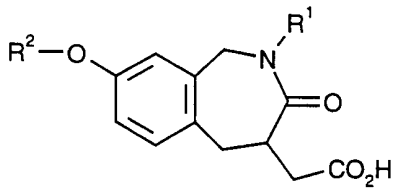
Feuerstein GZ, Stadel JM (1994) Osteopontin-stimulated vascular smooth muscle cell migration is mediated by β3 integrin. Exp Cell Res 214:459-464). The relative number of cells for optical density measurement was evaluated in parallel with counting the cells under microscope, and percentage of cells migrated was determined. Experiments were performed in triplicate.

It is to be understood that the invention is not limited to the embodiment illustrated hereinabove and the right is reserved to the illustrated embodiment and all modifications coming within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A method of treating stroke which comprises administering to a subject in need thereof an effective amount of a vitronectin receptor antagonist.

2. The method of claim 1 wherein the vitronectin receptor antagonist is a compound of formula (I):



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -NO_2, or tetrazolyl;

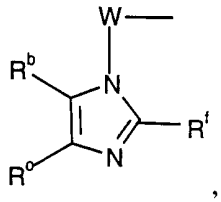
each R^8 independently is -OR', -NR'R", -NR'SO_2R', -NR'OR', or -$OCR'_2CO(O)R'$;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -$NR'R^{11}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is



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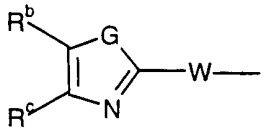

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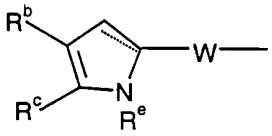
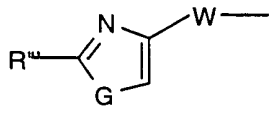
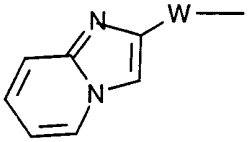
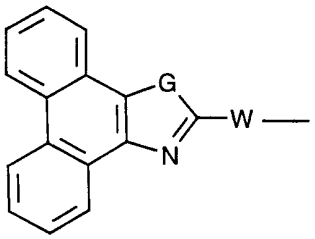
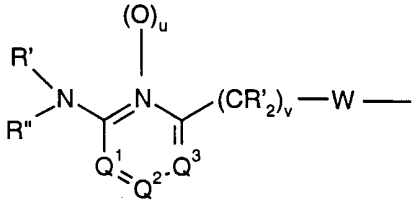
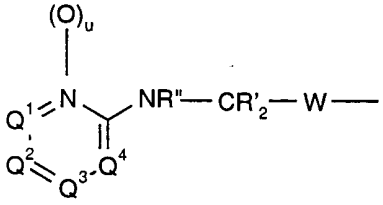
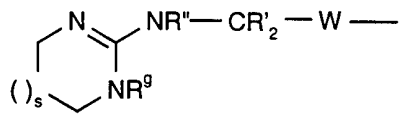








W is -(CHR^g)$_a$-U- (CHR^g)$_b$-;

U is absent or CO, CR$^g_2$, C(=CR$^g_2$), S(O)$_k$, O, NR^g, CR^{g}OR^g, CR^g(OR^k)CR$^g_2$, CR$^g_2$CR^g(OR^k), C(O)CR$^g_2$, CR$^g_2$C(O), CONR^i, NR^{i}CO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, NR^{g}C(S), S(O)$_2$NR^g, NR^{g}S(O)$_2$ N=N, NR^{g}NR^g, NR^{g}CR$^g_2$, CR$^g_2$NR^g, CR$^g_2$O, OCR$^g_2$, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C$_{1-6}$alkyl, Het-C$_{0-6}$alkyl, C$_{3-7}$cycloalkyl-C$_{0-6}$alkyl or Ar-C$_{0-6}$alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is is H, C$_{1-6}$alkyl, Het-C$_{0-6}$alkyl, C$_{3-7}$cycloalkyl-C$_{0-6}$alkyl, Ar- C$_{0-6}$alkyl, or C$_{1-6}$alkyl substituted by one to three groups chosen from halogen, CN, NR$^g_2$, OR^g, SR^g, CO$_2$R^g, and CON(R^g)$_2$;

R^f is H, C$_{1-6}$alkyl or Ar-C$_{0-6}$alkyl;

R^e is H, C$_{1-6}$alkyl, Ar-C$_{0-6}$alkyl, Het-C$_{0-6}$alkyl, C$_{3-7}$cycloalkyl-C$_{0-6}$alkyl, or (CH$_2$)$_k$CO$_2$R^g;

R^b and R^c are independently selected from H, C$_{1-6}$alkyl, Ar-C$_{0-6}$alkyl, Het-C$_{0-6}$alkyl, or C$_{3-6}$cycloalkyl-C$_{0-6}$alkyl, halogen, CF$_3$, OR^f, S(O)$_k$R^f, COR^f, NO$_2$, N(R^f)$_2$, CO(NR^f)$_2$, CH$_2$N(R^f)$_2$, or R^b and R^c are joined together to form a five or six

membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, -OR^g, -SR^g, -CN, -NR^gR^k, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$, or C_{1-6}alkyl optionally substituted by halo, -OR^g, -SR^g, -CN, -NR^gR", -NO_2, -CF_3, R'$S(O)_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

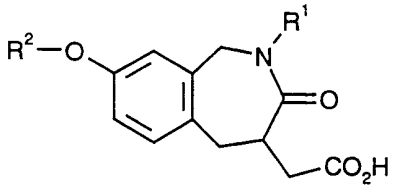
3. The method of claim 1 wherein the vitronectin receptor antagonist is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

4. The method of claim 1 wherein the vitronectin receptor antagonist is (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 wherein the vitronectin receptor antagonist is (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid or a pharmaceutically acceptable salt thereof.

6. The use of a vitronectin receptor antagonist in the manufacture of a medicament for the treatment of stroke.

7. The use according to claim 6 wherein the vitronectin receptor antagonist is a compound of formula (I):



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -NO_2, or tetrazolyl;

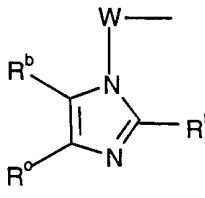
each R^8 independently is -OR', -NR'R", -NR'SO_2R', -NR'OR', or -$OCR'_2CO(O)R'$;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -$NR'R^{11}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is



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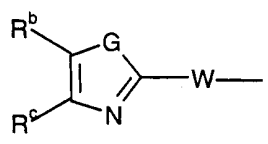

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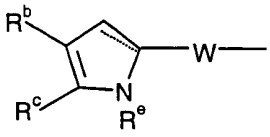
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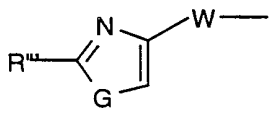
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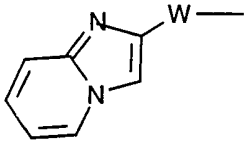
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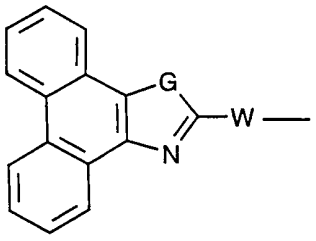
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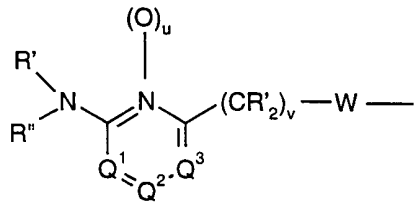
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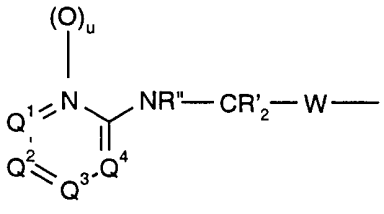
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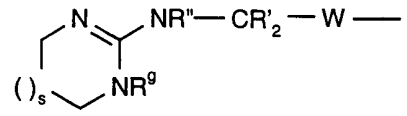
;

W is -$(CHR^g)_a$-U- $(CHR^g)_b$-;

U is absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, $CONR^i$, NR^iCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, NR^gNR^g, $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl, or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;

R^f is H, C_{1-6}alkyl or Ar-C_{0-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, or $(CH_2)_kCO_2R^g$;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six

membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, -OR^g, -SR^g, -CN, -NR^gR^k, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$, or C_{1-6}alkyl optionally substituted by halo, -OR^g, -SR^g, -CN, -NR^gR", -NO_2, -CF_3, R'S(O)$_r$-, -CO_2R^g, -COR^g or -$CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

8. The use according to claim 6 wherein the vitronectin receptor antagonist is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

9. The use according to claim 6 wherein the vitronectin receptor antagonist is (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

10. The use according to claim 6 wherein the vitronectin receptor antagonist is (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/21433

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 487/00, 401/12, 413/12, 417/12; A61K 31/44, 31/47
US CL :540/523; 514/211.05
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/523; 514/211.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE (1907-2000)
File Registry, File CAPlus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T,P	MILLER et al. Discover of Orally Active Nonpeptide Vironectin Receptor Antagonists Based on a 2-Benzazepine Gly-Asp Mimetic. Journal Medicinal Chemistry. 13 January 2000, Vol. 43, No. 1 , pages 22-26, see entire document.	1-10
T	WO 98/14192 A1 (SMITHKLINE BEECHAM CORPORATION) 09 April 1998 (09.04.98), especially pages 1-50, see entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 AUGUST 2000	Date of mailing of the international search report 29 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ALAN L. ROTMAN Telephone No. (703) 308-0196

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