The present invention can provide a therapeutic agent for gait disturbance that can be used safely in a patient with ischemic disease.

Brief Description of Drawing

[0021]

[Figure 1] Figure 1 shows an improvement effect on gait disturbance of 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide (which is hereinafter referred to as "compound A") in a rat ischemic gait disorder model. The vertical axis represents walking distance (m), and the horizontal axis represents the number of postoperative days (days), respectively. In the figure, a circle indicates a control~~sham surgery~~ group, a square indicates a sham surgery~~control~~ group, and a triangle indicates a compound A-administered group, respectively.

Description of Embodiment

[0022]

In the heterocyclic derivative (1), for example, it is preferable that:

R^1 and R^2 are the same or different and each represents phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, and alkoxy,

(1) A 5 or 6-membered aromatic ring group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom, and a sulfur atom or its benzene fused ring, wherein when the ring-constituting atoms are nitrogen or sulfur atoms, the nitrogen or sulfur atoms may form an oxide. Examples thereof can include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-indolyl, 2-furanyl, 3-furanyl, 3-benzofuranyl, 2-thienyl, 3-thienyl, 3-benzothienyl, 1,3-oxazole-2-yl, 4-isoxazolyl, 2-thiazolyl, 5-thiazolyl, 2-benzothiazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl, 1H-1,2, 4-triazole-1-yl, 1H-tetrazole-5-yl, 2H-tetrazole-5-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyrazolyl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyrazinyl, and 1,3,5-triazine-2-yl.

(2) A 4 to 8-membered saturated ring group or its benzene fused ring group containing the same or different 1 to 4 nitrogen, oxygen, or sulfur atoms as ring-constituting atoms, wherein when the ring-constituting atoms are nitrogen or sulfur atoms, the nitrogen or sulfur atoms may form an oxide. Examples thereof can include piperidino, piperazinyl, 3-methylpiperazine-1-yl, homopiperazinyl, morpnoholrino, thiomorpnoholrino, 1-pyrrolidinyl, 2-pyrrolidinyl, and 2-tetrahydrofuranyl.

[0037]

The heterocyclic derivative (1) can be synthesized by the method described in Patent Literature 1 (International Publication No. WO 02/088084).

Experimental Example 3: Improvement of gait disturbance in patient with arteriosclerosis obliterans

As a placebo-controlled, double-blind comparative study, Japanese patients with arteriosclerosis obliterans (selected by resting ABI, or the like) received placebo or selexipag (which is compound A) at 0.1 to 1.6 mg twice a day for 24 to 36 weeks (dose adjustment period: 8 to 20 weeks, dose maintenance period: 16 weeks).

[0083]

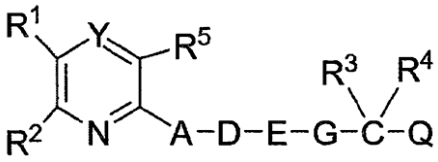
Improvement of patient's gait disturbance was confirmed using a treadmill, such as the maximum walking time (Gartner method).

Claims

[Claim 1]

A therapeutic agent for gait disturbance in a patient with ischemic disease, comprising a heterocyclic derivative represented by formula (1) below or a pharmaceutically acceptable salt thereof as an active component:

[Chem. 1]



(1)

wherein R^1 and R^2 are the same or different and each represents aryl optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro;

R^3 and R^4 are the same or different and each represents a hydrogen atom or alkyl;

R^5 represents a hydrogen atom, alkyl, or a halogen atom;

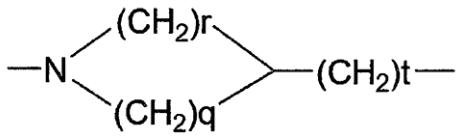
Y represents N or N -> O;

A represents NR^6 and R^6 represents a hydrogen atom, alkyl, alkenyl, or cycloalkyl; and

D represents alkylene or alkenylene optionally substituted with hydroxy, or A and D are combined with each

other to form a divalent group represented by formula (2) below:

[Chem. 2]

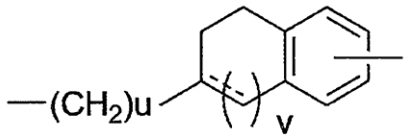


(2)

wherein r represents an integer of 0 to 2, q represents 2 or 3, and t represents an integer of 0 to 4; and

E represents phenylene or a single bond, or D and E are combined with each other to form a divalent group represented by formula (3) below:

[Chem. 3]



(3)

wherein

 represents a single bond or a double bond,

wherein u represents an integer of 0 to 2; v represents 0 or 1;

G represents O, S, SO, or SO_2; and

Q represents carboxy, alkoxycarbonyl, tetrazolyl, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, or a group represented by formula (4) below:

[Chem. 4]

$$—CONH—SO_2—R^7$$

(4)

wherein R^7 represents amino, monoalkylamino, dialkylamino, or hydroxy; or any of groups 1) to 4) below:

1) alkyl,

2) aryl,

3) aryloxy,

4) a heterocyclic group,

optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro.

[Claim 2]

The therapeutic agent for gait disturbance according to claim 1, wherein

in the heterocyclic derivative (1), R^1 and R^2 are the same or different and each represents phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, and alkoxy;

R^3 and R^4 are the same or different and each represents a hydrogen atom or alkyl;

R^5 is a hydrogen atom;

Y is N;

A is NR^6, R^6 is alkyl;

D is alkylene;

E is a single bond;

G is O; and

Q is carboxy or a group represented by formula (4), and R^7 is amino, monoalkylamino, dialkylamino, or hydroxy; or any of groups 1) to 4) below:

1) alkyl,

2) aryl,

3) aryloxy,

4) a heterocyclic group,

optionally substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano, and nitro.

[Claim 3]

The therapeutic agent for gait disturbance according to claim 1, wherein the patient with ischemic disease is a patient with arteriosclerosis obliterans.

[Claim 4]

The therapeutic agent for gait disturbance according to claim ~~1~~3, wherein the patient with arteriosclerosis obliterans is a patient classified into at least one selected from Fontaine Classifications I to IV.

[Claim 5]

A therapeutic agent for gait disturbance in a patient with ischemic disease, comprising 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}acetic acid or 2-{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide, or a pharmaceutically acceptable salt thereof as an active component.

[Claim 6]

The therapeutic agent for gait disturbance according to claim 5, wherein the patient with ischemic disease is a patient with arteriosclerosis obliterans.

[Claim 7]

The therapeutic agent for gait disturbance according to claim ~~5~~6, wherein the patient with arteriosclerosis obliterans is a patient classified into at least one selected from Fontaine Classifications I to IV.