Title: A PHARMACEUTICAL COMPOSITIONS CONTAINING LACTAM TYPE PYRIDINE DERIVATIVES AS AN EFFECTIVE INGREDIENT FOR THE PREVENTION AND TREATMENT OF ISCHEMIA

Abstract: The present invention relates to a pharmaceutical composition comprising a lactam type pyridine derivative for the prevention and treatment of ischemic diseases, more particularly to a pharmaceutical composition for preventing and treating ischemic diseases comprising a lactam type pyridine derivative or a pharmaceutically acceptable salt thereof as active ingredient, which provides superior cell-protecting effect and calcium homeostasis and HSP (heat shock protein) expression controlling effect.
[DESCRIPTION]

[Invention Title]

A PHARMACEUTICAL COMPOSITIONS CONTAINING LACTAM TYPE PYRIDINE DERIVATIVES AS AN EFFECTIVE INGREDIENT FOR THE PREVENTION AND TREATMENT OF ISCHEMIA

[Technical Field]

The present invention relates to pharmaceutical composition comprising a lactam type pyridine derivative effective in treating and preventing ischemic disease.

[Background Art]

Ischemic diseases including ischemic stroke and ischemic heart disease are caused by ischemia, which refers to the decrease in blood supply below a threshold value caused by the blocking of the cerebral artery or the coronary artery due to thrombosis or arteriosclerosis. As a result, brain and heart cells are damaged and die, resulting in brain infarction and myocardial infarction.

Thus, drugs that prevent the damage of cells caused by ischemia or facilitate regeneration thereof can be an ultimate treatment for ischemic brain disease or heart disease.

Ischemic heart diseases and cerebrovascular diseases, represented by myocardial infarction and stroke, are the first cause of death inside and outside Korea.

The drugs currently used for preventing and treating ischemic diseases include beta blockers, nitrates, calcium channel blockers, etc., which prevent the outbreak of ischemic diseases by reducing oxygen demand in the ischemic area or sustain a
therapeutic effect after the outbreak, thrombolytic agents, antithrombotic agents, anti-platelet agents, etc., which are used for reperfusion to the ischemic area after the ischemic outbreak, and the like.

Because these drugs are not satisfactory either in efficiency or safety, there has been a continued need for the development of new drugs for the treatment of ischemic disease with new mechanisms.

Recent studies on ischemic diseases focus on the development of a drug that can prevent or treat damaged cells and tissues following ischemia better than clotblusters or coagulation inhibitors, which are problematic in safety and acceptability.

At present, efforts are made with respect to the drugs that can protect death of cardiac myocytes from ischemia and reperfusion by acting on the Na⁺/H⁺-exchanger (NHE-1) and the K⁺-channel, which may be administered in combination with various ischemic drugs in order to inhibit the damage of cells and tissues in the ischemic area. With regard to stroke, developments of neuron-protecting agents that act on NMDA receptors, glycine receptors, and the like are carried out actively.

As heat shock proteins (HSP), adenosine receptor A1, etc., are known as possible targets in inhibiting cell death, researches on the above have been carried out recently.

The present invention is directed to the control of homeostasis of calcium, which is excessively released from the cytoplasm under ischemic condition and leads to cell death. HSP plays an important role in the control of calcium homeostasis. It has been known that calcium is excessively released under ischemic condition. Also, the level of expression of HSP increases under ischemic condition to provide cell-protecting effect. According to a recent report, the excessive release
of calcium induces the expression of the HSP27 protein, and the increased expression of HSP70 suppresses the excessive release of calcium. Therefore, it is probable that the exploration of a drug based on the relationship between calcium homeostasis and HSP expression may lead to the development of an ischemic disease treatment of new-concept.

However, there are not many reports about the substance for treating ischemic disease, which provides cell-protecting effect by controlling the intracellular expression and action of HSP under ischemic condition, controlling calcium homeostasis and improving cell viability.

The inventors of the present invention found that the lactam type pyridine derivatives (Korean Patent Publication Nos. 2005-69910, 2006-70945 and 2006-110764; Korean Patent Application No. 2005-127801) synthesized by them have an excellent effect of preventing and treating ischemic diseases through control of HSP expression and calcium homeostasis.

【Disclosure】


【Description of Drawings】
The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

FIG. 1 shows the confocal microscopic images for evaluating myocardial protecting effect through control of intracellular calcium homeostasis in Example 3;

FIG. 2 shows the photographs illustrating the change of the thickness of ventricular walls in an ischemic animal model in which rats underwent ligation of the distal left anterior descending coronary artery (Example 5) through TTC staining; and

FIG. 3 shows the photographs illustrating the change of the thickness of ventricular walls in an ischemic animal model in which rats underwent ligation of the distal left anterior descending coronary artery (Example 5) through H&E staining.

【Best Mode】

The present invention relates to a pharmaceutical composition for treating and preventing ischemic disease comprising a lactam type pyridine derivative represented by the following Chemical Formula 1 or a pharmaceutically acceptable salt thereof or a drug prepared therefrom:

【Chemical Formula 1】

\[
\text{In Chemical Formula 1,}
\]
 represents a single or double bond; each of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$

is independently selected from hydrogen, halo, cyano, nitro, $C_2$-$C_7$ acyl, hydroxy,

amino, $C_1$-$C_6$ alkyl, $C_3$-$C_9$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, $C_1$-$C_{10}$ alkylamino, $C_4$-$C_9$ cycloalkylamino, $C_4$-$C_9$ heterocycloalkylamino, arylamino, $C_1$-$C_6$ acylamino, $C_1$-$C_6$ acyloxy, $C_1$-$C_6$ alkylsulfanyl, $C_1$-$C_6$ alkylsulfonyl, $C_1$-$C_6$ alkylsulfonylamino, arylsulfanyl, arylsulfonic, arylsulfonamido, aryloxy, and heteroaryl, saturated heterocycle, aryl $C_1$-$C_{10}$ alkyl, heteroaryl $C_1$-$C_{10}$ alkyl, aryloxy and heteroaryloxy, or each of them may form a ring by bonding with a neighboring substituent; and $R_8$ is selected from hydrogen, $C_1$-$C_6$ alkyl, $C_3$-$C_9$ cycloalkyl, amino, $C_1$-$C_6$ aminoalkyl, $C_1$-$C_6$ alkyaminoo $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxyalkyl, carboxylic acid, carboxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyalkyl, $C_1$-$C_6$ alkoxyalkyl, $C_1$-$C_6$ alkyl, $C_2$-$C_7$ acyl, $C_2$-$C_7$ acyl $C_1$-$C_6$ alkyl, aryl, heteroaryl, saturated heterocycle, aryl $C_1$-$C_6$ alkyl and heteroaryl $C_1$-$C_6$ alkyl, or it may form a

ring by binding with the neighboring substituent $R_6$ or $R_7$;

wherein said aryl is selected from phenyl, naphthyl and fused phenyl; and each

of said saturated heterocycle and heteroaryl may be a pentagonal or hexagonal

saturated or unsaturated heterocyclic ring or a fused heterocyclic ring containing 1
to 3 hetero atoms selected from oxygen, nitrogen and sulfur, and each of said

saturated heterocycle, aryl and heteroaryl may be substituted with 1 to 4

substituents selected from hydrogen, halo, hydroxy, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy and

amino.

Preferably, in the lactam type pyridine derivative represented by Chemical

Formula 1,

each of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ is independently selected from hydrogen,

$C_1$-$C_6$ alkyl, $C_3$-$C_9$ cycloalkyl, $C_1$-$C_6$ alkoxy, phenyl $C_1$-$C_6$ alkyl, phenyl, saturated

heterocycle and heteroaryl; and

$R_8$ is selected from hydrogen, $C_1$-$C_6$ alkyl, amino, $C_1$-$C_6$ aminoalkyl, mono($C_1$-$C_6$

alkyl)amino $C_1$-$C_6$ alkyl, di($C_1$-$C_6$ alkyl)amino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$
alkoxyalkyl, carboxylic acid, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>7</sub> acyl, C<sub>2</sub>-C<sub>7</sub> acyl C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, phenyl C<sub>1</sub>-C<sub>6</sub> alkyl, saturated heterocycle, heteroaryl and heteroaryl C<sub>1</sub>-C<sub>6</sub> alkyl,

wherein each of said saturated heterocycle and heteroaryl is selected from furan, tetrahydrofuran, piperidine, pyrrolidine, morpholine, oxolane and benzodioxolane; and each of said saturated heterocycle, phenyl and heteroaryl is substituted with 1 to 4 substituents selected from hydrogen, halo, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy.

Specific examples of the lactam type pyridine derivative represented by Chemical Formula 1 according to the present invention include:

- Compound 1. 2H-[2,7]naphthyridine-1-one,
- Compound 2. 2-benzyl-2H-[2,7]naphthyridine-1-one,
- Compound 3. 3-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 4. 3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 5. 2-(4-methoxy-benzyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 6. 2-benzyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 7. 8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 8. 2,8-dimethyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 9. 2-ethyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 10. 2-benzyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 11. 8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 12. 2,8-dimethyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 13. 2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 14. 2-benzyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 15. 8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 16. 8-(4-fluoro-phenyl)-2,6-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 17. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 18. 8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 19. 8-(4-fluoro-phenyl)-2,6-dimethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 20. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 21. 6-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 22. 6-ethyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 23. 2,6-diethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 24. 2-(3,5-difluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 25. 2-(3,4-dimethoxy-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 26. 6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 27. 6-(3,4-difluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 28. 6-(3,4-difluoro-phenyl)-2-ethyl-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 29. 2-(4-fluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 30. 2-(3,5-dichloro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 31. 2-(3,5-difluoro-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 32. 2-(3,4-dimethoxy-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 33. 6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 34. 6-(4-fluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 35. 2-ethyl-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 36. 2-(3,5-difluoro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 37. 2-(3,4-dimethoxy-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 38. 2,6-bis-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 39. 2-(3,5-dichloro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 40. 6-(3,4-difluoro-phenyl)-2-(3,5-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 41. 6-(3,4-difluoro-phenyl)-2-(3,4-dimethoxy-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 42. 6-(3,4-difluoro-phenyl)-2-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 43. 2-(3,5-dichloro-phenyl)-6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 44. 6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 45. 2-ethyl-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 46. 6-isopropyl-2-(2-methoxy-ethyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 47. 2-(4-fluoro-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 48. 2-(3,4-dimethoxy-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 49. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 50. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester,

Compound 51. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 52. 6-tert-butyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 53. 6-tert-butyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 54. 6-tert-butyl-2-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 55. 6-tert-butyl-2-(4-fluoro-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 56. 6-tert-butyl-2-(3,4-dimethoxy-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 57. 2-(2-dimethylamino-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 58. 8-(4-fluoro-phenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 59. 8-(4-fluoro-phenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 60. 8-(4-fluoro-phenyl)-2-(2-hydroxy-ethyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 61. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid ethyl ester,

Compound 62. 8-(4-fluoro-phenyl)-6-methyl-2-pyridine-2-ylmethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 63. 2-[1,3]dioxolane-2-ylmethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 64. 2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 65. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid,

Compound 66. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid,

Compound 67. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid,
Compound 68. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester,

Compound 69. 2-ethyl-8-furan-2-yl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 70. 2-ethyl-6-methyl-8-(tetrahydro-furan-2-yl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 71. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid,

Compound 72. 2-ethyl-6,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 73. 2,8-diethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 74. 2-ethyl-8-isopropyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 75. 8-cyclopropyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 76. 8-cyclopentyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 77. 8-cyclohexyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 78. 8-benzo[1,3]dioxolane-5-yl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 79. 8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 80. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 81. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one.

Further, the lactam type pyridine derivative represented by Chemical Formula 1 may form a pharmaceutically acceptable salt with an acid, for example, hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, citric acid, fumaric acid, lactic acid, maleic acid, succinic acid and tartaric
acid. In addition, the lactam type pyridine derivative represented by Chemical Formula 1 may form a pharmaceutically acceptable salt by reacting with an alkali metal ion such as sodium, potassium, etc. or an ammonium ion.

Further, the pharmaceutical composition of the present invention may comprise, in addition to the lactam type pyridine derivative as active ingredient, a commonly used nontoxic pharmaceutically acceptable vehicle, adjuvant, excipient, or the like so as to be prepared into preparation forms for oral or parenteral administration common in the pharmaceutical field, for example, tablet, capsule, troche, liquid, suspension, etc. For oral administration, the composition may be prepared into tablet, capsule, solution, syrup, suspension, and the like. And, for parenteral administration, it may be prepared into abdominal, subcutaneous, intramuscular or transdermal injection form.

Further, the present invention encompasses a method for treating or preventing ischemic diseases comprising administering the compound represented by Chemical Formula 1 to a patient with a therapeutical dose capable of reducing cell death under ischemic condition.

As used in this description, the patient refers to a warm-blooded animal or mammal including human suffering from ischemic heart diseases and/or ischemic cerebrovascular diseases represented by angina pectoris, myocardial infarction, stroke and cerebrovascular dementia. Treatment of a ischemic disease patient means protection of cells and reduction of cell death of the patient. Diagnosis of a patient with an ischemic disease is within the ability and knowledge of those skilled in the art. A clinical doctor skilled in the related art can easily diagnose the disease based on clinical trials, medical checkup, health examination, family history, and the like.
The effective dose of the compound represented by Chemical Formula 1 can be easily determined based on the observation of results under similar conditions using common techniques. When determining the effective dose, various factors, including but not limited to, constitution, age and general health condition of the patient, degree or severity of the disease, response of the patient, the particular compound to be administered, mode of administration, bioavailability of the administered drug, selected route of administration and presence of jointly administered drug. A general dose for an adult patient whose body weight is 70 kg is 0.01 to 1000 mg/day. Based on the judgment of a doctor or a pharmacist, the dose may be administered once to several times a day at predetermined intervals. When treating a patient, the compound represented by Chemical Formula 1 may be administered by means of any mode or method, including oral and parenteral administration, that makes the compound biologically available at the effective dose. For example, the compound may be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally or rectally. Particularly, oral administration is preferred. Those skilled in preparing medical preparations can easily select an adequate form and mode of administration, considering the severity of disease or other situations.

The compound of the present invention may be administered in the form of a pharmaceutical composition or drug, which is prepared by mixing with a pharmaceutically acceptable vehicle or excipient. The mixing ratio and kind of the vehicle or excipient are determined depending on the selected route of administration and in accordance with the general standard pharmaceutical guidance. The pharmaceutical composition or drug is prepared by the methods known to those skilled in the pharmaceutical industry.
【Mode for Invention】

Therapeutic and preventive effects of the lactam type pyridine derivative represented by Chemical Formula 1 according to the present invention for ischemic diseases were identified. For specific methods of preparing the compounds represented by Chemical Formula 1 and drugs therefrom, refer to Korean Patent Publication Nos. 2005-69910, 2006-70945 and 2006-110764 and Korean Patent Application No. 2005-127801.

Example 1. Determination of HSP expression control

A 78-mer nucleotide sequence containing three repeating heat shock response elements (HSRE; GAANNTTC), an NheI site at the 5' end of the DNA sequence and a BglIII site at the 3' end (see the sequence below) and its complementary sequence were prepared. A double helical DNA was prepared by heating at 80 °C for 5 minutes and then annealing at room temperature.

5' -
GCCTCACGTCAGCTAGTGATGTTCTAGATCTAGAACATTCTAGCTAGAA
TGTTCTAAGATCTGACATGCTTAGC-3

* The italics correspond to NheI and BglIII sites, and the underlines correspond to the three repeating HSREs (GAANNTTC).

After digesting the ends with NheI and BglIII restriction enzymes, the resulting DNA sequence was introduced to a pLUC vector (BD Biosciences, San Jose, CA, USA). After transfection in *E. coli* DH5α and its culture thereof in a liquid medium (LB broth) containing ampicillin, the vector was isolated using a plasmid DNA prep kit (Qiagen, Hilden, Germany). The DNA sequence was identified by sequencing.
and the resultant vector was named as pHSR3. In order to introduce a neomycin resistance gene to the pHSR3 vector, a 1.5 kb DNA containing neomycin resistance gene ORF, SV40 early promoter, origin and polyA signal was produced by PCR using pcDNA3.1 plasmid (Invitrogen, Carlsbad, CA, USA) as template, and introduced into pHSR3 after BamHI single digestion. After transfection in E. coli DH5α and its culture thereof, a new plasmid vector pHSR3-neo was obtained. To prepare an established cell line therefrom, HeLa cells were transfected with lipofectamine (Invitrogen) when they were grown in a Petri dish to 60% to 80% confluent growth. Twenty four hours later, the cells were diluted along with the medium. After transferring to a new Petri dish, the medium was replaced by a medium containing G418. The cells were observed for 3 weeks, while exchanging the medium once every two days. Colonies exhibiting resistance to G418 were observed. The formed colonies were covered with a colony isolator, treated with trypsin and transferred to a 96-well plate, one per each. The cells were cultured using a medium containing G418 for 2 months, gradually transferring to a 24-well plate, to a 6-well plate, and finally to a Petri dish. Each prepared cell line was treated with each compound and was cultured in a CO₂ incubator. 24 hours later, luciferase activity was measured using a luciferase activity assay kit (BD Biosciences). The result is given in the following Table 1.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>HSP (fold increase)</th>
<th>Compounds</th>
<th>HSP (fold increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>2.59</td>
<td>Compound 42</td>
<td>1.11</td>
</tr>
<tr>
<td>Compound 2</td>
<td>2.53</td>
<td>Compound 43</td>
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<td>1.38</td>
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<td>1.02</td>
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<td>1.18</td>
<td>Compound 54</td>
<td>1.23</td>
</tr>
<tr>
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Example 2. Evaluation of protecting effect for primary cultured cardiac myocytes

In order to evaluate the effect of protecting cardiac myocytes, cardiac myocytes were isolated from the heart of a newborn rat and then cultured. Experiment was carried out as follows. The ventricular portion was taken from the heart and the red blood cells were removed in PBS (Dulbecco's phosphate-buffered saline solution) (pH 7.4, Gibco BRL). Using micro-dissecting scissors, the heart was minced in 10
mL of collagenase I (0.8 mg/mL, 262 units/mg, Gibco BRL) solution until the pieces were approximately 1 mm³ and treated at 37 °C for 15 minutes. The supernatant (collagenase I solution) was collected and the remaining tissues were treated with fresh collagenase I solution and left alone at 37 °C for 15 minutes. The collected supernatant was diluted in α-MEM (Gibco BRL) containing 10% FBS (fetal bovine serum). The diluted supernatant was centrifuged at 1200 rpm, for 4 minutes at room temperature. The precipitated cell pellets were resuspended in α-MEM medium containing 5 mL of 10% FBS.

The above procedure was repeated for about 10 to 15 times until the tissue morphology was changed. In order to reduce contamination of fibroblasts, the suspended cells were collected and cultured in a 100 mm tissue culture dish for 2 hours at 37 °C.

The cells not adhering to the tissue culture dish were collected again and cultured after being distributed to a 96-well plate at 1×10⁴ cells/well. After culturing for 4 to 6 hours and washing twice with culture medium, 0.1 µM bromodeoxyuridine (BrdU) was added thereto. The cells were cultured at 37 °C in a 5% CO₂ incubator.

After culturing overnight in a 96-well plate, the cells were put in an airtight humidified chamber containing 5% CO₂, 5% H₂ and 85% N₂ (anaerobic system, Technomart INC, Seoul, Korea). After washing twice with deaerated serum-free α-MEM and adding the test compound, 200 µL of the medium was added thereto and hypoxia condition was maintained for 12 hours at 37 °C.

Twelve hours later, the medium was removed and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide solution (MTT bromide solution) (Sigma, St. Louis, MO) was added to each well until the final concentration was 0.5 mg/mL. Then, it
was cultured at 37 °C for 2 hours so as the MTT reaction to occur. The formazan crystal produced in each well was dissolved by adding dimethyl sulfoxide (DMSO) and absorbance was measured at 570 nm using a spectrophotometer. The result is given in the following Table 2.

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<th>Compounds</th>
<th>Cell viability (%)</th>
<th>Compound</th>
<th>Cell viability (%)</th>
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Example 3. Evaluation of effect of myocardial protection through control of calcium homeostasis

The level of cytosolic free Ca\(^{2+}\) was measured by confocal microscopic analysis. Cardiac myocytes of newborn white rats were cultured for 24 hours in a 4-well plate (1×10\(^5\) cells/well) coated with 1.5% gelatin, using 10% FBS α-MEM containing 0.1 μM BrdU.

24 hours later, the cells were washed twice with serum-free medium, and treated at room temperature with fluo-4 with a final concentration of 2 μM along with 500 μL of medium per well. Then, after treating in a 37 °C incubator for 20 minutes, the cells were washed with PBS and covered with a cover slide after adding PBS to prevent them from drying. Fluorescence images were taken from the light emitted through a 510 to 560 nm bandpass filter, upon activated at 488 nm by argon
laser. The relative change of free intracellular Ca\textsuperscript{2+} was determined based on the fluorescence intensity. The result is shown in FIG. 1.

Example 4. Evaluation of heart protecting effect

In order to find out how the test compounds protect the heart from ischemia, anti-ischemic effects were investigated in white rats as follows.

Male white rats (300 to 450 g, Orient, Seoul, Korea) were anesthetized by injecting sodium pentobarbital (100 mg/kg) intra-abdominally. After intravenous injection of heparin (1000 U/kg), the heart was collected by ablation. Specifically, a cannula (PE 240) was inserted and artificial respiration was performed using a rodent ventilator. Under that condition, an aortic cannula was inserted in the aorta and the heart was ablated under retrograde perfusion. The extracted heart was hung on Langendorff apparatus quickly and unnecessary tissues on the heart were removed. Perfusion was induced under static pressure (85 mmHg) with 37 °C modified Krebs-Henseleit bicarbonate buffer [composition (mM/L): 116 NaCl, 4.7 KCl, 1.1 MgSO\textsubscript{4}, 1.17 KH\textsubscript{2}PO\textsubscript{4}, 24.9 NaHCO\textsubscript{3}, 2.52 CaCl\textsubscript{2}, 8.32 glucose, 2.0 pyruvate] saturated with 95% O\textsubscript{2}/5% CO\textsubscript{2}. A metal cannula to which a latex balloon filled with an ethanol-distilled water mixture (1:1 vol/vol) was linked, was inserted in the left ventricle through the pulmonary vein. Then, the left ventricular pressure transmitted through the balloon was transduced by using a pressure transducer, and amplified by using an isovolumetric amplifier (Plugsys bridge amplifier). Then, the pressure was recorded in a recorder (Linearcorder mark 8 WR 3500). Thereafter, the heart was stabilized for 15 minutes. Then, left ventricular end-diastolic pressure (LVEDP) was given by 5 mmHg and such volume of the balloon was kept through the experiments.
Baseline cardiac contractile function, heart rate (HR) and coronary flow (CF) were measured. Cardiac contractile function was calculated by subtracting left ventricular peak systolic pressure (LVSP) from left ventricular end diastolic pressure (LVEDP), yielding left ventricular developed pressure (LVDP). Double product RPP (rate-pressure product), another important parameter for indirectly assessing cardiac performance in Langendorff heart, in which cardiac output could not be measured ordinarily, was calculated by multiplying HR by LVDP. Total coronary blood flow was measured by the use of a coronary flow probe (diameter: 1.0 mm) installed in the aortic cannula with an electromagnetic flowmeter. Temperature of the heart was steadily maintained throughout the experiment by immersing the heart at 37 °C in physiological saline solution to which 95% O₂ /5% CO₂ was constantly supplied. After stabilization, the heart was perfused for 10 minutes with vehicle (0.04% DMSO) only or a test compound with a specific concentration or the control material in the vehicle. Thereafter, cardiac contractile function, HR, and CF were measured again. Global ischemia was induced by completely shutting off the perfusate for 30 minutes. Severity of ischemia was determined as the time to contracture (TTC, min) during global ischemia in which the first 5 mmHg increase in LVEDP was observed. Then, the heart was perfused and, 30 minutes later, contractile functions (LVDP, HR and CF) were measured again. After reperfusion was accomplished for 30 minutes, the concentration of lactate dehydrogenase (LDH) in the reperfusate was measured with a kit as a sensitive index for ischemic myocardial damage. The result is given in the following Table 3.

【Table 3】
Example 5. Activity analysis in an ischemic animal model under ligation of distal left anterior descending coronary artery

Myocardial infarction was induced in white rats through ligation of the distal left anterior descending coronary artery. A cannula was inserted into an 8-week-old male Sprague Dawley rat (weighing about 250 g) anesthetized with ketamine (1 mL/rat). Positive pressure circulation (180 mL/min) was maintained using a Harvard ventilator with indoor air containing oxygen (2 L/min). About 2 cm of the left side of the heart of the rat was cut open. After ligating the left anterior descending artery with 7-0 silk suture, the rat was bred for 3 days under normal conditions. The test compound was injected abdominally immediately after the ligation of the left anterior descending artery, and for 3 days, once a day, at a dose of 10 mg/kg. The compound had been dissolved in water for injection containing 5%
DMSO and 2% Tween-20 and heated at 70 °C before the injection. Effect of the compound under ischemic condition could be identified from the color change of the cardiac muscle 3 days after the treatment. To this end, TTC (triphenyltetrazolium chloride) staining was carried out. H&E staining was carried out in order to measure the change of the ventricular wall thickness. As a result, it was identified that the test compounds of the present invention resulted in reduced infarction area as compared to the control material. The result is shown in FIG. 2 and FIG. 3.

[Industrial Applicability]

As explained hereinbefore, the lactam type pyridine derivative represented by Chemical Formula 1 according to the present invention showed excellent HSP expression controlling and cardiac myocyte protecting activities, excellent myocardial protection activity through control of intracellular calcium homeostasis, and good result in an ischemic animal model under ligation of the distal left anterior descending coronary artery.

Accordingly, the lactam type pyridine derivative represented by Chemical Formula 1 is useful in preventing and treating ischemic diseases, specifically ischemic heart diseases and ischemic cerebrovascular diseases represented by angina pectoris, myocardial infarction, stroke and cerebrovascular dementia.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying drawings.
[CLAIMS]

[Claim 1]

A pharmaceutical composition for treating and preventing ischemic disease comprising a lactam type pyridine derivative represented by the following Chemical Formula 1 or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]

wherein

- represents a single or double bond; each of R1, R2, R3, R4, R5, R6 and R7 is independently selected from hydrogen, halo, cyano, nitro, C2-C7 acyl, hydroxy, amino, C1-C6 alkyl, C3-C9 cycloalkyl, C2-C6 alkenyl, C1-C6 alkoxy, C1-C6 alkylthio, C1-C10 alkylamino, C4-C9 cycloalkylamino, C4-C9 heterocycloalkylamino, arylamino, C1-C6 acylamino, C1-C6 acyloxy, C1-C6 alkylsulfanyl, C1-C6 alkylsulfonyl, C1-C6 alkylsulfonylamino, arylsulfanyl, arylsulfonyl, arylsulfonylamino, aryl, heteroaryl, saturated heterocycle, aryl C1-C10 alkyl, heteroaryl C1-C10 alkyl, arylxyloxy and heteroaryloxy, or each of them may form a ring by bonding with a neighboring substituent; and

R8 is selected from hydrogen, C1-C6 alkyl, C3-C9 cycloalkyl, amino, C1-C6 aminoalkyl, C1-C6 alkylamino C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkoxyalkyl, carboxylic acid, carboxy C1-C6 alkyl, C1-C6 alkoxy carbonyl, C1-C6 alkoxy carbonyl C1-C6 alkyl, C2-C7 acyl, C2-C7 acyl C1-C6 alkyl, aryl, heteroaryl, saturated heterocycle,

25
aryl C₁-C₆ alkyl and heteroaryl C₁-C₆ alkyl, or it may form a ring by binding with the neighboring substituent R₆ or R₇,

wherein said aryl is selected from phenyl, naphthyl and fused phenyl; and each of said saturated heterocycle and heteroaryl may be a pentagonal or hexagonal saturated or unsaturated heterocyclic ring or a fused heterocyclic ring containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur, and each of said saturated heterocycle, aryl and heteroaryl is substituted with 1 to 4 substituents selected from hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy and amino.

[Claim 2]

The pharmaceutical composition as set forth in claim 1,

wherein each of R₁, R₂, R₃, R₄, R₅, R₆, and R₇ is independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₉ cycloalkyl, C₁-C₆ alkoxy, phenyl C₁-C₆ alkyl, phenyl, saturated heterocycle and heteroaryl; and

R₈ is selected from hydrogen, C₁-C₆ alkyl, amino, C₁-C₆ aminoalkyl, mono(C₁-C₆ alkyl)amino C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxyalkyl, carboxylic acid, carboxy C₁-C₆ alkyl, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkoxy carbonate C₁-C₆ alkyl, C₂-C₇ acyl, C₂-C₇ acyl C₁-C₆ alkyl, phenyl, phenyl C₁-C₆ alkyl, saturated heterocycle, heteroaryl and heteroaryl C₁-C₆ alkyl,

wherein each of said saturated heterocycle and heteroaryl is selected from furan, tetrahydrofuran, piperidine, pyrrolidine, morpholine, oxolane and benzodioxolane; and each of said saturated heterocycle, phenyl and heteroaryl is substituted with 1 to 4 substituents selected from hydrogen, halo, hydroxy, C₁-C₆ alkyl and C₁-C₆ alkoxy.
【Claim 3】

The pharmaceutical composition as set forth in claim 1, wherein the lactam type pyridine derivative represented by Chemical Formula 1 comprises:

- Compound 1. 2H-[2,7]naphthyridine-1-one,
- Compound 2. 2-benzyl-2H-[2,7]naphthyridine-1-one,
- Compound 3. 3-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 4. 3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 5. 2-(4-methoxy-benzyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 6. 2-benzyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 7. 8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 8. 2,8-dimethyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 9. 2-ethyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 10. 2-benzyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 11. 8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 12. 2,8-dimethyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 13. 2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 14. 2-benzyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 15. 8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,
- Compound 16. 8-(4-fluoro-phenyl)-2,6-dimethyl-2H-[2,7]naphthyridine-1-one,
- Compound 17. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,
- Compound 18. 8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 19. 8-(4-fluoro-phenyl)-2,6-dimethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 20. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 21. 6-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 22. 6-ethyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 23. 2,6-diethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 24. 2-(3,5-difluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 25. 2-(3,4-dimethoxy-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 26. 6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 27. 6-(3,4-difluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 28. 6-(3,4-difluoro-phenyl)-2-ethyl-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 29. 2-(4-fluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 30. 2-(3,5-dichloro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 31. 2-(3,5-difluoro-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 32. 2-(3,4-dimethoxy-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 33. 6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 34. 6-(4-fluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,
Compound 35. 2-ethyl-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 36. 2-(3,5-difluoro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 37. 2-(3,4-dimethoxy-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 38. 2,6-bis-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 39. 2-(3,5-dichloro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 40. 6-(3,4-difluoro-phenyl)-2-(3,5-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 41. 6-(3,4-difluoro-phenyl)-2-(3,4-dimethoxy-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 42. 6-(3,4-difluoro-phenyl)-2-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 43. 2-(3,5-dichloro-phenyl)-6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 44. 6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 45. 2-ethyl-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 46. 6-isopropyl-2-(2-methoxy-ethyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 47. 2-(4-fluoro-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 48. 2-(3,4-dimethoxy-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 49. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 50. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester,

Compound 51. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 52. 6-tert-butyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 53. 6-tert-butyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 54. 6-tert-butyl-2-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 55. 6-tert-butyl-2-(4-fluoro-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 56. 6-tert-butyl-2-(3,4-dimethoxy-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 57. 2-(2-dimethylamino-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 58. 8-(4-fluoro-phenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 59. 8-(4-fluoro-phenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 60. 8-(4-fluoro-phenyl)-2-(2-hydroxy-ethyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 61. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid ethyl ester,

Compound 62. 8-(4-fluoro-phenyl)-6-methyl-2-pyridine-2-ylmethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 63. 2-[1,3]dioxolane-2-ylmethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 64. 2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 65. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid,

Compound 66. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid,

Compound 67. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid,

Compound 68. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester,

Compound 69. 2-ethyl-8-furan-2-yl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 70. 2-ethyl-6-methyl-8-(tetrahydro-furan-2-yl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 71. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid,

Compound 72. 2-ethyl-6,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 73. 2,8-diethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 74. 2-ethyl-8-isopropyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 75. 8-cyclopropyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 76. 8-cyclopentyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 77. 8-cyclohexyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 78. 8-benzo[1,3]dioxolane-5-yl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 79. 8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 80. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 81. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one, or
a pharmaceutically acceptable salt thereof.

[Claim 4]

A drug for preventing and treating ischemic diseases comprising a lactam type pyridine derivative represented by the Chemical Formula 1 or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]

wherein

- represents a single or double bond; each of R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is independently selected from hydrogen, halo, cyano, nitro, C₂-C₇ acyl, hydroxy,
amino, C₁-C₆ alkyl, C₃-C₉ cycloalkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₁₀ alkylamino, C₄-C₉ cycloalkylamino, C₄-C₉ heterocycloalkylamino, arylamino, C₁-C₈ acylamino, C₁-C₆ acyloxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylsulfonylamino, arylsulfanyl, arylsulfonyl, arylsulfonlamino, aryl, heteroaryl, saturated heterocycle, aryl C₁-C₁₀ alkyl, heteroaryl C₁-C₁₀ alkyl, arylxy and heteroarylxy, or each of them may form a ring by bonding with a neighboring substituent; and

R₈ is selected from hydrogen, C₁-C₆ alkyl, C₃-C₉ cycloalkyl, amino, C₁-C₆ aminoalkyl, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxyalkyl, carboxylic acid, carboxy C₁-C₆ alkyl, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkoxy carbonyl C₁-C₆ alkyl, C₂-C₇ acyl, C₂-C₇ acyl C₁-C₆ alkyl, aryl, heteroaryl, saturated heterocycle, aryl C₁-C₆ alkyl and heteroaryl C₁-C₆ alkyl, or it may form a ring by bonding with the neighboring substituent R₆ or R₇,

wherein said aryl is selected from phenyl, naphthyl and fused phenyl; and each of said saturated heterocycle and heteroaryl may be a pentagonal or hexagonal saturated or unsaturated heterocyclic ring or a fused heterocyclic ring containing 1 to 3 hetero atoms selected from oxygen, nitrogen and sulfur, and each of said saturated heterocycle, aryl and heteroaryl is substituted with 1 to 4 substituents selected from hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy and amino.

[Claim 5]
The drug as set forth in claim 4,

wherein each of R₁, R₂, R₃, R₄, R₅, R₆, and R₇ is independently selected from hydrogen, C₁-C₆ alkyl, C₃-C₉ cycloalkyl, C₁-C₆ alkoxy, phenyl C₁-C₆ alkyl, phenyl, saturated heterocycle and heteroaryl; and
R₈ is selected from hydrogen, C₁-C₆ alkyl, amino, C₁-C₆ aminoalkyl, mono(C₁-C₆ alkyl)amino C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxyalkyl, carboxylic acid, carboxy C₁-C₆ alkyl, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkoxy carbonyl C₁-C₆ alkyl, C₂-C₇ acyl, C₂-C₇ acyl C₁-C₆ alkyl, phenyl, phenyl C₁-C₆ alkyl, saturated heterocycle, heteroaryl and heteroaryl C₁-C₆ alkyl,

wherein each of said saturated heterocycle and heteroaryl is selected from furan, tetrahydrofuran, piperidine, pyrrolidine, morpholine, oxolane and benzodioxolane; and each of said saturated heterocycle, phenyl and heteroaryl is substituted with 1 to 4 substituents selected from hydrogen, halo, hydroxy, C₁-C₆ alkyl and C₁-C₆ alkoxy.

[Claim 6]

The drug as set forth in claim 4, wherein the lactam type pyridine derivative represented by Chemical Formula 1 comprises:

- Compound 1. 2H-[2,7]naphthyridine-1-one,
- Compound 2. 2-benzyl-2H-[2,7]naphthyridine-1-one,
- Compound 3. 3-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 4. 3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 5. 2-(4-methoxy-benzyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 6. 2-benzyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
- Compound 7. 8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 8. 2,8-dimethyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 9. 2-ethyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 10. 2-benzyl-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
- Compound 11. 8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 12. 2,8-dimethyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 13. 2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 14. 2-benzyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 15. 8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 16. 8-(4-fluoro-phenyl)-2,6-dimethyl-2H-[2,7]naphthyridine-1-one,
Compound 17. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,
Compound 18. 8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 19. 8-(4-fluoro-phenyl)-2,6-dimethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 20. 2-ethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,
Compound 21. 6-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 22. 6-ethyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 23. 2,6-diethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 24. 2-(3,5-difluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
Compound 25. 2-(3,4-dimethoxy-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,
Compound 26. 6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 27. 6-(3,4-difluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,
Compound 28. 6-(3,4-difluoro-phenyl)-2-ethyl-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 29. 2-(4-fluoro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compounds 30. 2-(3,5-dichloro-phenyl)-8-methyl-6-phenyl-2H-[2,7]naphthyridine-1-one,

Compound 31. 2-(3,5-difluoro-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 32. 2-(3,4-dimethoxy-phenyl)-8-(4-fluoro-phenyl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 33. 6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 34. 6-(4-fluoro-phenyl)-2,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 35. 2-ethyl-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 36. 2-(3,5-difluoro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 37. 2-(3,4-dimethoxy-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 38. 2,6-bis-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 39. 2-(3,5-dichloro-phenyl)-6-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 40. 6-(3,4-difluoro-phenyl)-2-(3,5-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 41. 6-(3,4-difluoro-phenyl)-2-(3,4-dimethoxy-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,
Compound 42. 6-(3,4-difluoro-phenyl)-2-(4-fluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 43. 2-(3,5-dichloro-phenyl)-6-(3,4-difluoro-phenyl)-8-methyl-2H-[2,7]naphthyridine-1-one,

Compound 44. 6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 45. 2-ethyl-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 46. 6-isopropyl-2-(2-methoxy-ethyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 47. 2-(4-fluoro-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 48. 2-(3,4-dimethoxy-phenyl)-6-isopropyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 49. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 50. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester,

Compound 51. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid methyl ester,

Compound 52. 6-tert-butyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 53. 6-tert-butyl-2-methyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 54. 6-tert-butyl-2-ethyl-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,
Compound 55. 6-tert-butyl-2-(4-fluoro-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 56. 6-tert-butyl-2-(3,4-dimethoxy-phenyl)-8-piperidine-1-yl-2H-[2,7]naphthyridine-1-one,

Compound 57. 2-(2-dimethylamino-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 58. 8-(4-fluoro-phenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 59. 8-(4-fluoro-phenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 60. 8-(4-fluoro-phenyl)-2-(2-hydroxy-ethyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 61. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid ethyl ester,

Compound 62. 8-(4-fluoro-phenyl)-6-methyl-2-pyridine-2-ylmethyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 63. 2-[1,3]dioxolane-2-ylmethyl-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 64. 2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluoro-phenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 65. [8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-acetic acid,

Compound 66. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-carboxylic acid,
Compound 67. 8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-carboxylic acid,

Compound 68. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthyridine-2-yl]-propionic acid methyl ester.

Compound 69. 2-ethyl-8-furan-2-yl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 70. 2-ethyl-6-methyl-8-(tetrahydro-furan-2-yl)-3,4-dihydro-2H-[2,7]naphthyridine-1-one,

Compound 71. 3-[8-(4-fluoro-phenyl)-6-methyl-1-oxo-1H-[2,7]naphthyridine-2-yl]-propionic acid,

Compound 72. 2-ethyl-6,8-dimethyl-2H-[2,7]naphthyridine-1-one,

Compound 73. 2,8-diethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 74. 2-ethyl-8-isopropyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 75. 8-cyclopropyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 76. 8-cyclopentyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 77. 8-cyclohexyl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 78. 8-benzo[1,3]dioxolane-5-yl-2-ethyl-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 79. 8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 80. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-2H-[2,7]naphthyridine-1-one,

Compound 81. 2-ethyl-8-(4-fluoro-piperidine-1-yl)-6-methyl-3,4-dihydro-2H-[2,7]naphthyridine-1-one, or

a pharmaceutically acceptable salt thereof.
[Claim 7]

The drug as set forth in any of claims 4 to 6, wherein the ischemic diseases include ischemic heart diseases and ischemic cerebrovascular diseases.

[Claim 8]

The drug as set forth in any of claims 4 to 6, wherein the ischemic disease is angina pectoris.

[Claim 9]

The drug as set forth in any of claims 4 to 6, wherein the ischemic disease is myocardial infarction.

[Claim 10]

The drug as set forth in any of claims 4 to 6, wherein the ischemic disease is stroke.

[Claim 11]

The drug as set forth in any of claims 4 to 6, wherein the ischemic disease is cerebrovascular dementia.

[Claim 12]

The drug as set forth in claim 7, which is prepared into a form suitable to be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally or rectally.
【Claim 13】

The drug as set forth in claim 12, which is prepared in the form of a tablet, an ointment or an injection.
Drawings

Fig.1

Control  Hypoxia  Compound No. 8  Compound No. 25
(24 hr)

Compound No. 65  Compound No. 66  Compound No. 71  Compound No. 74
Fig.2

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<th>Ligation (72 hr)</th>
<th>Compound No. 8</th>
<th>Compound No. 25</th>
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<td>LV wall (cm)</td>
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<td>0.8</td>
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<td>LV/RV (w/w)</td>
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Fig. 3

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<th>Normal</th>
<th>Ligation (72 hr)</th>
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<tr>
<td>Wall Thickness (cm)</td>
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<td>0.5 0.4 0.1</td>
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</tbody>
</table>

<table>
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<tr>
<th>Compound No. 65</th>
<th>Compound No. 66</th>
<th>Compound No. 74</th>
<th>Compound No. 76</th>
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</thead>
<tbody>
<tr>
<td>Wall Thickness (cm)</td>
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<td>0.6 0.5 0.1</td>
<td>0.7 0.5 0.1</td>
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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/4375(2006.01)i

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)

IPC 8 A61K and C07D

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)

eKIPASS, STN (Registry and Capitus), Pubmed

* Key words: chemical structure in claims, pyridine, naphtalhydrin, lactam, ischemia, CNS, cardiac, angina pectoris

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

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

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
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  "P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search
02 JULY 2008 (02.07.2008)

Date of mailing of the international search report
02 JULY 2008 (02.07.2008)

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