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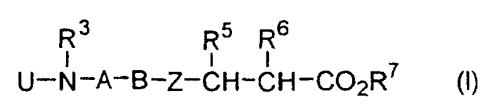
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(54) **ARYL-SUBSTITUTED ALICYCLIC COMPOUND AND MEDICAL COMPOSITION COMPRISING THE SAME**

(57) An aryl-substituted alicyclic compound of the formula (I):



wherein U is 1,4,5,6-tetrahydropyrimidin-2-yl, etc., A is phenylene, etc., B is piperidine-1,4-diyl, etc., Z is

-CONH-, etc., R³ is hydrogen, etc., R⁵ is hydrogen, aryl, etc., R⁶ is a mono-substituted amino (e.g., benzyloxy-carbonylamino), R⁷ is hydrogen, etc., and a process for preparation thereof, and a pharmaceutical composition containing the same. The compound of the present invention has a high selectivity for αvβ3 integrin, and exhibits a potent inhibitory activity thereto, and hence, it is useful as a preventive or/and a therapeutic agent for a disease in which αvβ3 integrin is involved.

EP 1 371 646 A1

Description

TECHNICAL FIELD

5 **[0001]** The present invention relates to a novel aryl-substituted alicyclic compound having $\alpha v\beta 3$ integrin inhibitory activity, etc., and a pharmaceutical composition containing the same.

BACKGROUND ART

10 **[0002]** Integrin is a family of receptors that have cell adhesion molecules as ligands, and mediate cell-to-cell and cell-to-extracellular matrix adhesions. Integrins directly participate in preservation of cell shape, anchorage for cell migration, and intra- and extracellular signal transduction. Therefore, integrins play important roles in a range of biological events including cell survival, movement, proliferation, development and differentiation.

15 **[0003]** Integrin is a heterodimeric transmembrane glycoprotein consisting of α and β chains. To date, various kinds of α and β chains have been known, and thus more than 20 integrins have been identified based on combination of the α and β chains (Trends Pharmacol., Sci., 21, 29 (2000)). In addition to the integrins, a number of cell adhesion molecules including, proteins that constitute extracellular matrix such as, collagen and vitronectin, proteins involved in immune and/or inflammatory cells adhesion such as, VCAM- 1 and ICAM-1, and proteins involved in blood coagulation such as, fibrinogen and von Willebrand factor have been identified as integrin ligands (Cell, 69, 11 (1992)).

20 **[0004]** The $\alpha v\beta 3$ integrin comprising αv - and $\beta 3$ -chains is also known as vitronectin receptor. Although vitronectin is the main ligand for $\alpha v\beta 3$ integrin, some other proteins with RGD sequence such as fibronectin, fibrinogen and osteopontin are also known as $\alpha v\beta 3$ integrin ligands.

25 **[0005]** It is known that $\alpha v\beta 3$ integrin is expressed on a wide variety of adhesive cells. Among them, much attention has been given to the pathophysiological role of $\alpha v\beta 3$ integrin expressed on cells where cell adhesion, migration, or proliferation is activated with the development of disease state. For example, after angioplasty, abnormal migration and proliferation of vascular smooth muscle cells often causes neointimal hyperplasia resulting in restenosis. Similarly, in cancer tissues, abnormal migration and proliferation of vascular endothelial cells accelerates angiogenesis. Moreover, it has been shown in animal models of progressive diseases that the expression of $\alpha v\beta 3$ integrin is increased in defective cells, and that disease symptoms can be prevented by administration of antibodies or synthetic peptides which inhibit $\alpha v\beta 3$ integrin (Curr. Pharm. Des., 3, 545 (1997)). Therefore, it is suggested that $\alpha v\beta 3$ integrin may play an important role in the initiation and progression of restenosis and angiogenesis. Besides these two conditions, $\alpha v\beta 3$ integrin has also been shown to be involved in other diseases including osteoporosis, rheumatoid arthritis, cancer metastasis, diabetic retinopathy, inflammatory diseases and viral infections (Curr. Biol., 3, 596 (1993); Cell. Mol. Life Sci., 56, 427 (1999); Drug Discovery Today, 5, 397 (2000)).

30 **[0006]** From the information above, it is assumed that inhibition of $\alpha v\beta 3$ integrin might cure diseases that are accompanied with cells adhesion, migration or proliferation. Therefore, it is expected that $\alpha v\beta 3$ integrin inhibitors may be useful as a novel type of antiestenotic agents, antiarteriosclerotic agents, anticancer agents, antiosteoporosis agents, antiinflammatory agents, antiimmune agents, and agents for eye diseases.

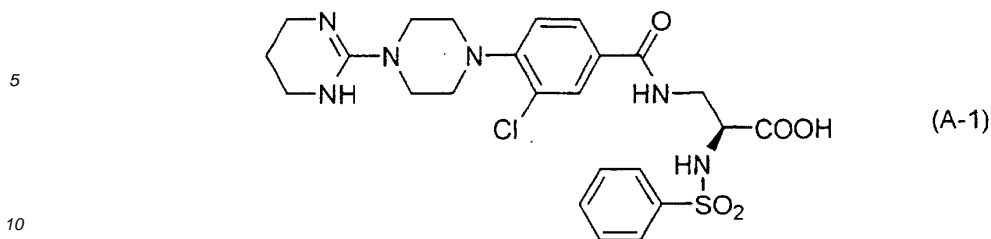
35 **[0007]** Beside $\alpha v\beta 3$ integrin, $\alpha IIb\beta 3$ integrin or GPIIb/IIIa, another integrin closely related to $\alpha v\beta 3$ integrin, has been shown to be highly involved in platelet aggregation. As inhibitors of $\alpha v\beta 3$ integrin that also suppress $\alpha IIb\beta 3$ integrin may cause breeding adverse effects, and may be inappropriate for repeated administration, $\alpha v\beta 3$ integrin inhibitors with high selectivity for $\alpha v\beta 3$ integrin as opposed to $\alpha IIb\beta 3$ integrin have long been desired.

40 **[0008]** As far as the present inventors know, no therapeutic agent with highly selective $\alpha v\beta 3$ integrin inhibitory activity has, so far, been developed. Therefore, under the present situation where diseases that involve $\alpha v\beta 3$ integrin have been increasing with the aging population, it is necessary to develop inhibitors with high selectivity for $\alpha v\beta 3$ integrin as opposed to $\alpha IIb\beta 3$ integrin.

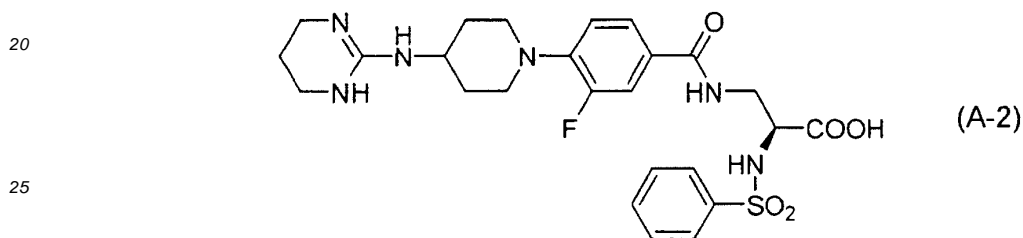
45 **[0009]** To date, quite a lot of compounds having $\alpha v\beta 3$ integrin inhibitory activity have been reported (cf. USP 5990145, WO 98/18461, WO 99/38849, WO99/52872, etc.)

50 **[0010]** For example, WO 99/38849 discloses (2S)-2-benzenesulfonylamino-3-[3-chloro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)piperazin-1-yl]benzoylamino]propanoic acid represented by the following formula (A-1, Example 59), and it reports that this compound has a potent $\alpha v\beta 3$ integrin inhibitory activity (IC₅₀ value: 3.5 nM) and GPIIb/IIIa inhibitory activity (IC₅₀ value: 0.2 nM or less).

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15 [0011] In addition, WO 99/52872 discloses (2S)-2-benzenesulfonylamino-3-[3-fluoro-4-[[4-(1,4,5,6-tetrahydropyrimidin-2-yl)amino]-piperidin-1-yl]benzoylamino]propanoic acid represented by the following formula (A-2, Example 52), and it reports that this compound has a potent $\alpha\beta 3$ integrin inhibitory activity (IC_{50} value: 1.0 nM or less) and GPIIb/IIIa inhibitory activity (IC_{50} value: 1.0 nM or less).

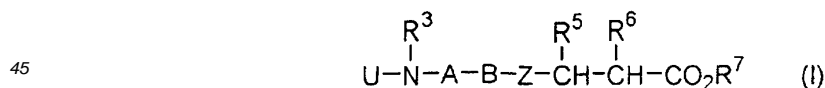


30 [0012] However, the chemical structures of these compounds are completely different from those of the compounds of the present invention as described below, and these compounds have a potent GPIIb/IIIa inhibitory activity, which is also different from the compounds of the present invention.

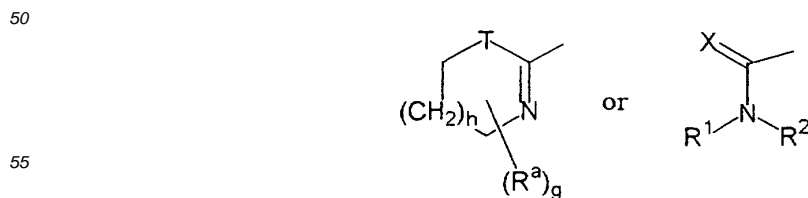
35 [0013] The present inventors have intensively studied, and have found that a novel aryl-substituted alicyclic compound of the formula (I) has a potent $\alpha\beta 3$ integrin inhibitory activity, and that it is useful as a preventive or therapeutic agent for diseases with which $\alpha\beta 3$ integrin is involved, and have accomplished the present invention.

DISCLOSURE OF INVENTION

40 [0014] The present invention provides an aryl-substituted alicyclic compound of the following formula (I), a prodrug thereof, a pharmaceutically acceptable salt thereof or an N-oxide derivative thereof, or a hydrate or a solvate thereof, a process for preparing these compounds, and a pharmaceutical composition containing the same.

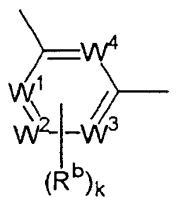


wherein U is a group of the following formula:



A is a group of the following formula:

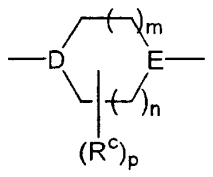
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B is a group of the following formula:

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Z is $-\text{CONR}^4(\text{CH}_2)_q-$, $-\text{NR}^4\text{CO}(\text{CH}_2)_q-$ or $-\text{COCH}_2(\text{CH}_2)_q-$,

T is $-\text{CH}_2-$, an oxygen atom, a sulfur atom or $-\text{NR}^d$,

X is an oxygen atom or a sulfur atom,

W^1 , W^2 , W^3 and W^4 are the same or different, and each is $-\text{CH}-$ or a nitrogen atom,

D and E are the same or different, and each is $-\text{CH}-$ or a nitrogen atom, R^a is the same or different, and each is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group, an aralkyl group, a

30

C_{1-6} alkyloxy group, a C_{1-6} alkyloxycarbonyl group, a formyl group, a C_{1-6} alkylcarbonyl group, a carboxyl group, a C_{1-6} alkylcarbonyloxy group, an amino group, a C_{1-3} alkylamino group, a di(C_{1-3} alkyl)amino group, a formylamino group, a C_{1-3} alkylcarbonylamino group, an arylcarbonylamino group, a nitro group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group or a trifluoroethoxy group, or

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when two R^a groups attach to the same carbon atom, then they combine to form an oxo group or a thioxo group, or together with said carbon atom to form a spiro ring,

R^b is the same or different, and each is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group, an aralkyl group, a

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C_{1-6} alkyloxy group, a C_{1-6} alkyloxycarbonyl group, a formyl group, a C_{1-6} alkylcarbonyl group, a carboxyl group, a C_{1-6} alkylcarbonyloxy group, an amino group, a C_{1-3} alkylamino group, a di(C_{1-3} alkyl)amino group, a formylamino group, a C_{1-3} alkylcarbonylamino group, an arylcarbonylamino group, a nitro group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group or a trifluoroethoxy group,

R^c is the same or different, and each is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group, an aralkyl group, a

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C_{1-6} alkyloxy group, a C_{1-6} alkyloxycarbonyl group, a formyl group, a C_{1-6} alkylcarbonyl group, a carboxyl group, a C_{1-6} alkylcarbonyloxy group, an amino group, a C_{1-3} alkylamino group, a di(C_{1-3} alkyl)amino group, a formylamino group, a C_{1-3} alkylcarbonylamino group, an arylcarbonylamino group, a nitro group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group or a trifluoroethoxy group,

or two R^c groups may combine to form $-(\text{CR}^8\text{R}^9)_i-$,

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R^d is a hydrogen atom, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group, an aralkyl group, a formyl group, a C_{1-6} alkylcarbonyl group or a C_{1-6} alkyloxycarbonyl group,

R^1 and R^2 are the same or different, and each is a hydrogen atom, a C_{1-10} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group, an aralkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkylsulfonyl group or an arylsulfonyl group,

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or R^1 and R^2 may combine to form $-(\text{CR}^{10}\text{R}^{11})_u-$ or $-(\text{CH}_2)_v\text{Y}(\text{CH}_2)_w-$,

R^3 and R^4 are the same or different, and each is a hydrogen atom, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, an aryl group or an aralkyl group,

R^5 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl

group, an aryl group or an aralkyl group,

R⁶ is a hydrogen atom, a halogen atom, a hydroxy group, a C₁₋₆ alkyl group, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, an aryl group, an aralkyl group, a C₁₋₆ alkyloxy group, a C₃₋₇ cycloalkyloxy group, a C₂₋₆ alkenyloxy group, a C₂₋₆ alkynyloxy group, an aryloxy group, an aralkyloxy group, a C₁₋₆ alkylcarbonyloxy group, a C₃₋₇ cycloalkylcarbonyloxy group, a C₂₋₆ alkenylcarbonyloxy group, a C₂₋₆ alkynylcarbonyloxy group, an arylcarbonyloxy group, an aralkylcarbonyloxy group, an amino group or a monosubstituted amino group (in which the substituent is a formyl, a C₁₋₁₀ alkylcarbonyl, a C₃₋₇ cycloalkylcarbonyl, a C₂₋₁₀ alkenylcarbonyl, a C₂₋₁₀ alkynylcarbonyl, an arylcarbonyl, an aralkylcarbonyl, a C₇₋₁₅ polycyclo-C₀₋₃ alkylcarbonyl, a C₁₋₁₆ alkyloxy carbonyl, a polyfluoro-C₁₋₁₆ alkyloxy carbonyl, a C₃₋₇ cycloalkyloxy carbonyl, a C₂₋₁₆ alkenyloxy carbonyl, a C₂₋₁₆ alkynyloxy carbonyl, an aryloxy carbonyl, a C₃₋₇ cycloalkyl-C₁₋₆ alkyloxy carbonyl, an aralkyloxy carbonyl, a C₁₋₁₀ alkylaminocarbonyl, a C₃₋₇ cycloalkylaminocarbonyl, a C₂₋₁₀ alkenylaminocarbonyl, a C₂₋₁₀ alkynylaminocarbonyl, an arylaminocarbonyl, an aralkylaminocarbonyl, a C₁₋₁₀ alkylsulfonyl, a C₃₋₇ cycloalkylsulfonyl, a C₂₋₁₀ alkenylsulfonyl, a C₂₋₁₀ alkynylsulfonyl, an arylsulfonyl, an aralkylsulfonyl, a C₇₋₁₅ polycyclo-C₀₋₃ alkylsulfonyl, a

C₁₋₁₀ alkylaminosulfonyl, a C₃₋₇ cycloalkylaminosulfonyl, a C₂₋₁₀ alkenylaminosulfonyl, a C₂₋₁₀ alkynylaminosulfonyl, an arylaminosulfonyl or an aralkylaminosulfonyl),

R⁷ is a hydrogen atom, a C₁₋₆ alkyl group, a C₃₋₇ cycloalkyl group, an aryl group or an aralkyl group,

R⁸, R⁹, R¹⁰ and R¹¹ are the same or different, and each is a hydrogen atom, a C₁₋₃ alkyl group or an aryl group,

Y is an oxygen atom, a sulfur atom or -NR¹²-,

R¹² is a hydrogen atom, a C₁₋₆ alkyl group, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, an aryl group, an aralkyl group, a

C₁₋₆ alkylcarbonyl group or a C₁₋₆ alkyloxy carbonyl group,

g is an integer of 1 to 4,

h is an integer of 0 to 3,

k is an integer of 1 to 3,

m and n are the same or different, and each is an integer of 0 to 3, but the sum of m and n should be an integer of 1 to 3, p is an integer of 1 to 4,

q is 0 or 1,

t is an integer of 1 to 3,

u is an integer of 3 to 7,

v and w are the same or different, and each is an integer of 1 to 4, but the sum of v and w should be an integer of 2 to 6, provided that (i) when E is a nitrogen atom, then Z is -CONR⁴(CH₂)_q- or -COCH₂(CH₂)_q-, (ii) in the above definition, the alkyl group, the cycloalkyl group, the alkenyl group, the alkynyl group, and the alkyl moiety of the aralkyl group may optionally be substituted by 1 to 3 atoms or groups selected from a halogen, a C₁₋₆ alkyloxy, an amino and a hydroxy, and the aryl group and the aryl moiety may optionally be substituted by 1 to 5 atoms or groups selected from a halogen, a C₁₋₆ alkyl, a C₃₋₇ cycloalkyl, an aryl, an aralkyl, an amino, an amino-C₁₋₆ alkyl, a formylamino, a C₁₋₃ alkylcarbonylamino, a C₁₋₆ alkylamino, a C₁₋₆ alkylamino-C₁₋₆ alkyl, a di(C₁₋₆ alkyl)amino, a di(C₁₋₆ alkyl)amino-C₁₋₆ alkyl, an arylcarbonylamino, a C₁₋₆ alkylaminocarbonylamino, an arylaminocarbonylamino, a C₁₋₄ alkyloxy, a C₁₋₄ alkylthio, a C₁₋₄ alkylsulfonyl, a

C₁₋₄ alkyloxy-C₁₋₆ alkyl, a carboxyl, a carboxyl-C₁₋₆ alkyl, a C₁₋₄ alkyloxy carbonyl, a hydroxy, a hydroxy-C₁₋₆ alkyl, a cyano, a trifluoromethyl, a trifluoromethoxy, a C₁₋₄ alkylcarbonyloxy and a nitro.

[0015] The prodrug of the compound of the formula (I) means a compound of the formula (I) wherein R⁷ is a hydrogen atom, and the carboxyl group is modified, said modified carboxyl group being converted into a carboxyl group by enzymatically or chemical cleavage in a living body, for example, such as compounds having an esterified carboxyl group. The esterified carboxyl group is preferably ones being used in the preparation of prodrugs in the pharmaceutical field, for example, a C₁₋₆ alkyloxy carbonyl group, a C₃₋₇ cycloalkyloxy carbonyl group, an aryloxy carbonyl group, an aralkyloxy carbonyl group, an optionally substituted C₁₋₃ alkyloxy carbonyl group (the substituent is selected from a carboxyl, a C₁₋₃ alkyloxy carbonyl, a C₁₋₃ alkylaminocarbonyl, a di(C₁₋₃ alkyl)aminocarbonyl, a C₁₋₃ alkylamino, a di(C₁₋₃ alkyl)amino, a C₁₋₃ alkyloxy or a dioxolenyl), or a group: -COOCHR^eOCOR^f (R^e is a C₁₋₃ alkyl group, and R^f is a C₁₋₆ alkyl group, a C₃₋₇ cycloalkyl group, an aryl group, an aralkyl group, a C₁₋₆ alkyloxy group, a C₃₋₇ cycloalkyloxy group, an aryloxy group or an aralkyloxy group). Besides, it is apparent that the compound of the formula (I) wherein R⁷ is other than a hydrogen atom may fall under the category of prodrug. Suitable examples of prodrug are hereinafter disclosed.

[0016] The pharmaceutically acceptable salt of the compound of the formula (I) includes a pharmaceutically acceptable acid addition salt of the compound of the formula (I) having a group being capable of producing an acid addition salt within the structure thereof or a prodrug thereof, or a pharmaceutically acceptable salt with a base of the compound of the formula (I) having a group being capable of producing a salt with a base within the structure thereof or a prodrug thereof. Suitable acid addition salts are, for example, a salt with an inorganic acid such as hydrochloride, hydrobromide, hydroiodide, sulfate, perchlorate, phosphate, etc., and a salt with an organic acid such as oxalate, malonate, maleate,

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