(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 371 646 A1

(12) EUROPEAN PATENT APPLICATION
published in accordance with Art. 158(3) EPC

(43) Date of publication:
17.12.2003 Bulletin 2003/51

(21) Application number: **02705159.8**

(22) Date of filing: **14.03.2002**

(51) Int Cl.[7]: **C07D 211/62**, C07D 401/12, C07D 413/14, C07D 239/14, C07D 233/50, C07D 243/04, C07D 401/14, A61K 31/506, A61K 31/551, A61K 31/445, A61K 31/497, A61K 31/4545, A61P 43/00, A61P 9/00, A61P 19/00, A61P 9/10, A61P 29/00, A61P 19/02, A61P 35/00, A61P 27/02, A61P 17/06

(86) International application number:
PCT/JP02/02391

(87) International publication number:
WO 02/074743 (26.09.2002 Gazette 2002/39)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **19.03.2001 JP 2001079029**

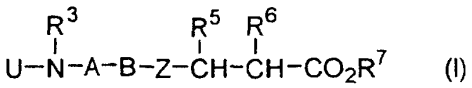
(71) Applicant: **Dainippon Pharmaceutical Co., Ltd.**
Osaka-shi, Osaka 541-8524 (JP)

(72) Inventors:
- **MORIE, Toshiya**
  Matsubara-shi, Osaka 580-0024 (JP)
- **IWAMA, Seiji**
  Kishiwada-shi, Osaka 596-0078 (JP)
- **NOTAKE, Mitsue**
  Suita-shi, Osaka 565-0825 (JP)
- **KITANO, Tomoko**
  Tondabayashi-shi, Osaka 584-0031 (JP)

(74) Representative: **Coleiro, Raymond et al**
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

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

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



(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., R^3 is hydrogen, etc., R^5 is hydrogen, aryl, etc., R^6 is a mono-substituted amino (e,g., benzyloxycarbonylamino), R^7 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

Printed by Jouve, 75001 PARIS (FR)

Description

TECHNICAL FIELD

[0001] The present invention relates to a novel aryl-substituted alicyclic compound having αvβ3 integrin inhibitory activity, etc., and a pharmaceutical composition containing the same.

BACKGROUND ART

[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.

[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)).

[0004] The αvβ3 integrin comprising αv- and β3-chains is also known as vitronectin receptor. Although vitronectin is the main ligand for αvβ3 integrin, some other proteins with RGD sequence such as fibronectin, fibrinogen and osteopontin are also known as αvβ3 integrin ligands.

[0005] It is known that αvβ3 integrin is expressed on a wide variety of adhesive cells. Among them, much attention has been given to the pathophysiological role of αvβ3 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 αvβ3 integrin is increased in defective cells, and that disease symptoms can be prevented by administration of antibodies or synthetic peptides which inhibit αvβ3 integrin (Curr. Pharm. Des., 3, 545 (1997)). Therefore, it is suggested that αvβ3 integrin may play an important role in the initiation and progression of restenosis and angiogenesis. Besides these two conditions, αvβ3 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)).

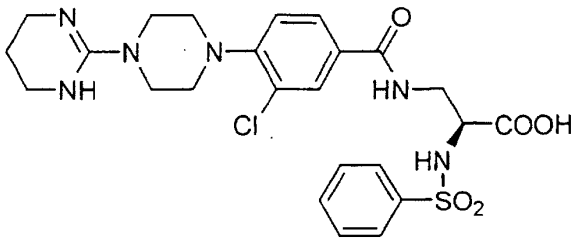
[0006] From the information above, it is assumed that inhibition of αvβ3 integrin might cure diseases that are accompanied with cells adhesion, migration or proliferation. Therefore, it is expected that αvβ3 integrin inhibitors may be useful as a novel type of antirestenotic agents, antiarteriosclerotic agents, anticancer agents, antiosteoporosis agents, antiinflammatory agents, antiimmune agents, and agents for eye diseases.

[0007] Beside αvβ3 integrin, αIIbβ3 integrin or GPIIb/IIIa, another integrin closely related to αvβ3 integrin, has been shown to be highly involved in platelet aggregation. As inhibitors of αvβ3 integrin that also suppress αIIbβ3 integrin may cause breeding adverse effects, and may be inappropriate for repeated administration, αvβ3 integrin inhibitors with high selectivity for αvβ3 integrin as opposed to αIIbβ3 integrin have long been desired.

[0008] As far as the present inventors know, no therapeutic agent with highly selective αvβ3 integrin inhibitory activity has, so far, been developed. Therefore, under the present situation where diseases that involve αvβ3 integrin have been increasing with the aging population, it is necessary to develop inhibitors with high selectivity for αvβ3 integrin as opposed to αIIbβ3 integrin.

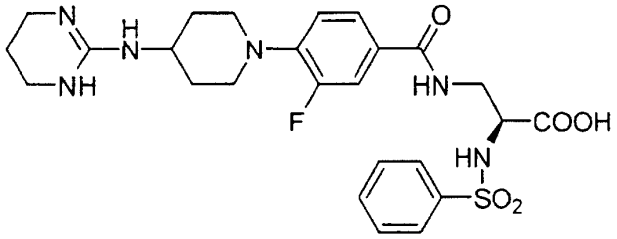
[0009] To date, quite a lot of compounds having αvβ3 integrin inhibitory activity have been reported (cf. USP 5990145, WO 98/18461, WO 99/38849, WO99/52872, etc.)

[0010] For example, WO 99/38849 discloses (2S)-2-benzenesulfonylamino-3-[3-chloro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)piperazin-I-yl]benzoylamino]propanoic acid represented by the following formula (A-1, Example 59), and it reports that this compound has a potent αvβ3 integrin inhibitory activity (IC_{50} value: 3.5 nM) and GPIIb/IIIa inhibitory activity (IC_{50} value: 0.2 nM or less).



(A-1)

[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 αvβ3 integrin inhibitory activity (IC_{50} value: 1.0 nM or less) and GPIIb/IIIa inhibitory activity (IC_{50} value: 1.0 nM or less).



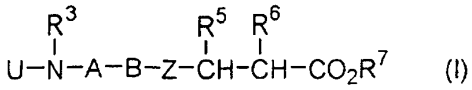
(A-2)

[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.

[0013] The present inventors have intensively studied, and have found that a novel aryl-substituted alicyclic compound of the formula (I) has a potent αvβ3 integrin inhibitory activity, and that it is useful as a preventive or therapeutic agent for diseases with which αvβ3 integrin is involved, and have accomplished the present invention.

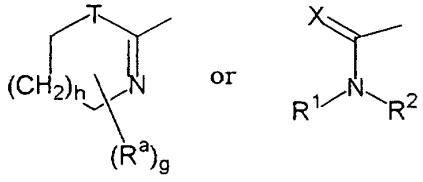
DISCLOSURE OF INVENTION

[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.



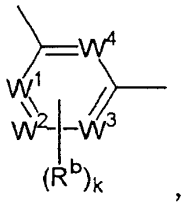
(I)

wherein U is a group of the following formula:

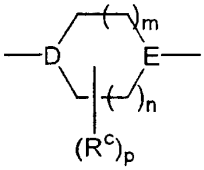


,

A is a group of the following formula:



B is a group of the following formula:



Z is $-CONR^4(CH_2)_q-$, $-NR^4CO(CH_2)_q-$ or $-COCH_2(CH_2)_q-$,
T is $-CH_2-$, an oxygen atom, a sulfur atom or $-NR^d-$,
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 -CH- or a nitrogen atom,
D and E are the same or different, and each is -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 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
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 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 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 $-(CR^8R^9)_t-$,
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,
or R^1 and R^2 may combine to form $-(CR^{10}R^{11})_u-$ or $-(CH_2)_vY(CH_2)_w-$,
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,
R^6 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 C_{1-6} alkyloxy group, a C_{3-7} cycloalkyloxy group, a C_{2-6} alkenyloxy group, a C_{2-6} alkynyloxy group, an aryloxy group, an aralkyloxy group, a C_{1-6} alkylcarbonyloxy group, a C_{3-7} cycloalkylcarbonyloxy group, a C_{2-6} alkenylcarbonyloxy group, a C_{2-6} alkynylcarbonyloxy group, an arylcarbonyloxy group, an aralkylcarbonyloxy group, an amino group or a monosubstituted amino group (in which the substituent is a formyl, a C_{1-10} alkylcarbonyl, a C_{3-7} cycloalkylcarbonyl, a C_{2-10} alkenylcarbonyl, a C_{2-10} alkynylcarbonyl, an arylcarbonyl, an aralkylcarbonyl, a C_{7-15} polycyclo-C_{0-3} alkylcarbonyl, a C_{1-16} alkyloxycarbonyl, a polyfluoro-C_{1-16} alkyloxycarbonyl, a C_{3-7} cycloalkyloxycarbonyl, a C_{2-16} alkenyloxycarbonyl, a C_{2-16} alkynyloxycarbonyl, an aryloxycarbonyl, a C_{3-7} cycloalkyl-C_{1-6} alkyloxycarbonyl, an aralkyloxycarbonyl, a C_{1-10} alkylaminocarbonyl, a C_{3-7} cycloalkylaminocarbonyl, a C_{2-10} alkenylaminocarbonyl, a C_{2-10} alkynylaminocarbonyl, an arylaminocarbonyl, an aralkylaminocarbonyl, a C_{1-10} alkylsulfonyl, a C_{3-7} cycloalkylsulfonyl, a C_{2-10} alkenylsulfonyl, a C_{2-10} alkynylsulfonyl, an arylsulfonyl, an aralkylsulfonyl, a C_{7-15} polycyclo-C_{0-3} alkylsulfonyl, a
C_{1-10} alkylaminosulfonyl, a C_{3-7} cycloalkylaminosulfonyl, a C_{2-10} alkenylaminosulfonyl, a C_{2-10} alkynylaminosulfonyl, an arylaminosulfonyl or an aralkylaminosulfonyl),
R^7 is a hydrogen atom, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, an aryl group or an aralkyl group,
R^8, R^9, R^{10} and R^{11} are the same or different, and each is a hydrogen atom, a C_{1-3} alkyl group or an aryl group,
Y is an oxygen atom, a sulfur atom or $-NR^{12}-$,
R^{12} 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
C_{1-6} alkylcarbonyl group or a C_{1-6} alkyloxycarbonyl 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 $-CONR^4(CH_2)_q-$ or $-COCH_2(CH_2)_q-$, (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 C_{1-6} 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 C_{1-6} alkyl, a C_{3-7} cycloalkyl, an aryl, an aralkyl, an amino, an amino-C_{1-6} alkyl, a formylamino, a C_{1-3} alkylcarbonylamino, a C_{1-6} alkylamino, a C_{1-6} alkylamino-C_{1-6} alkyl, a di(C_{1-6} alkyl)amino, a di(C_{1-6} alkyl)amino-C_{1-6} alkyl, an arylcarbonylamino, a C_{1-6} alkylaminocarbonylamino, an arylaminocarbonylamino, a C_{1-4} alkyloxy, a C_{1-4} alkylthio, a C_{1-4} alkylsulfonyl, a
C_{1-4} alkyloxy-C_{1-6} alkyl, a carboxyl, a carboxyl-C_{1-6} alkyl, a C_{1-4} alkyloxycarbonyl, a hydroxy, a hydroxy-C_{1-6} alkyl, a cyano, a trifluoromethyl, a trifluoromethoxy, a C_{1-4} alkylcarbonyloxy and a nitro.

[0015] The prodrug of the compound of the formula (I) means a compound of the formula (I) wherein R^7 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 C_{1-6} alkyloxycarbonyl group, a C_{3-7} cycloalkyloxycarbonyl group, an aryloxycarbonyl group, an aralkyloxycarbonyl group, an optionally substituted C_{1-3} alkyloxycarbonyl group (the substituent is selected from a carboxyl, a C_{1-3} alkyloxycarbonyl, a C_{1-3} alkylaminocarbonyl, a di(C_{1-3} alkyl)aminocarbonyl, a C_{1-3} alkylamino, a di(C_{1-3} alkyl)amino, a C_{1-3} alkyloxy or a dioxolenyl), or a group: $-COOCHR^eOCOR^f$ (R^e is a C_{1-3} alkyl group, and R^f is a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, an aryl group, an aralkyl group, a C_{1-6} alkyloxy group, a C_{3-7} cycloalkyloxy group, an aryloxy group or an aralkyloxy group). Besides, it is apparent that the compound of the formula (I) wherein R^7 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,

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.