Complete Specification

SPECIFICATION
Polycyclic Carbamoylpyridone Derivative Having HIV Integrase Inhibitory Activity
[Technical Field]
[0001]
The present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing" an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.
[Background Art]
[0002]
Among viruses, human immunodeficiency virus (HIV), a kind of retrovirus, is known to cause acquired immunodeficiency syndrome (AIDS). The therapeutic agent for AIDS is mainly selected from a group of reverse transcriptase inhibitors (e.g., AZT, 3TC) and protease inhibitors (e.g., Indinavir), but they are proved to be accompanied by side effects such as nephropathy and the emergence of resistant viruses. Thus, the development of anti-HIV agents having the other mechanism of action has been desired.
On the other hand, a combination therapy is reported to be efficient in treatment for AIDS because of the frequent emergence of the resistant mutant. Reverse transcriptase inhibitors and protease inhibitors are clinically used as an anti-HIV agent, however agents having the same mechanism of action often exhibit cross-resistance or only an additional activity. Therefore, anti-HIV agents having the other mechanism of action are desired.
Under the circumstances above, an HIV integrase inhibitor has been focused on as an anti-HIV agent having a novel mechanism of action (Ref: Patent Documents 1 and 2) . As an anti-HIV agent having such a mechanism of action, known are carbamoyl-substituted hydroxypyrimidinone derivative (Ref: Patent Documents 3 and 4) and carbamoyl-substituted hydroxypyrrolidione derivative (Re£ Patent Document 5). Further, a patent application concerning carbamoyl-substituted hydroxypyridone derivative has been filed (Ref: Patent Document 6, Example 8) .
Other known carbamoylpyridone derivatives include 5-alkoxypyridine-3-carboxamide derivatives and X -pyrone-3-carboxamide derivatives, which are a plant growth inhibitor or herbicide (Ref: Patent Documents 7-9).
Other HIV integrase inhibitors include N-containing condensed cyclic compounds

1

(Ref- Patent Document 10).
(Patent Document I]WO03/0166275
[Patent Document 2]WO2004/024693
[Patent Document 3]WO03/035076
[Patent Document 4]WO03/035076
[Patent Document 5]WO2004/0O4657
[Patent Document 6]JP Patent Application 2003-32772
[Patent Document 7]JP Patent Publication 1990-108668
[Patent Document 8]JP Patent Publication 1990-108683
[Patent Document 9jJP Patent Publication 1990-96506
[Patent Document 10]WO2005/016927
[Disclosure of Invention]
[Problem to be Solved by the Invention]
[0003]
The development of a novel integrase inhibitor has been desired.
[Means to Solve the Problem]
[0004]
The present inventors have intensively studied to find that a novel polycyclic carbamoylpyridone derivative possesses a potent HIV integrase inhibitory activity. Moreover, the present inventors have discovered that a compound of the present invention and a pharmaceutical composition containing the same are useful as an antiviral agent, an antiretroviral agent, an anti-HIV agent, an anti-HTLV-1 (Human T cell leukemia virus type I) agent, an anti-FIV (Feline immunodeficiency virus) agent or an anti-SIV (Simian immunodeficiency virus) agent, especially an anti-HIV agent or anti-AIDS agent, to accomplish the present invention shown below.

2

2

Rl is hydrogen, optionally substituted lower allcyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower al/venyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO2, NRa (Ra is hydrogen or lower alkyl), -N= and =N-)), O or CUV
Z2 is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from O, S, SO, SO2, NR5 (Rfl is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy or optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO2. NR° (Rs is selected independently from the same substituent group as R'O, "N= and =N-)), -N^ or =N-
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from 0, S, SO, S02and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom.'
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted
3

lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino;
R4 and Z2part taken together forms a ring, where the compound (I) is represented by the following formula (1-1), or (I-II):

(wherein,
A ring is optionally substituted heterocycle;
R14 and Rx are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted eycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from 0, S, SO, SO2. NRfi (R5 is selected independently from the same substituent group as R'O, "N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxyearbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;
4

a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, Rxis not present;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from 0, S, SO, SOa and N H, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group!
R- is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)

(wherein,
D ring is optionally substituted heterocycle;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from O, S, SO, SO2 and N H, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)), its pharmaceutically acceptable salt, or solvate thereof.
(2) A compound according to the above (I), pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen.
(3) A compound according to the above (I), pharmaceutically acceptable salt, or
5

solvate thereof, wherein X is lower alkylene; R2 is phenyl or phenyl substituted with at least halogen.
(4) A compound according to the above (I), pharmaceutically acceptable salt, or solvate thereof, wherein R3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
(5) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R;> is hydrogen.
(6) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen or lower alkyl; X is lower alkylenei R2 is phenyl or phenyl substituted with at least halogen,' R;1 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
(7) A compound of the formula-

(wherein,
A ring is optionally substitiited heterocycle.'
R1'1 and Rx are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or
6

lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO2. NR5 (R5 is selected independently from the same substituent group as R'1), ~N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloaikylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyL'
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, Rx is not present;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from O, S, SO, SO2 and N H, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group."
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or solvate thereof
(8) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen or lower alkyl; X is lower alkylene; Ra is phenyl or phenyl substituted with at least halogen.' R3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
(9) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.
(10) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein Rx is hydrogen; R1'1 is hydrogen or optionally substituted lower alkyl.
7

(11) A compound according- to the above (7), pharmaceutical^ acceptable salt, or solvate thereof, wherein A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s).
(12) A compound of the formula-

(wherein,
A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s);
the stereochemistry of an asymmetric carbon represented by * shows R- or S~ configuration, or a mixture thereof.
R1'1 and Rx are independently hydrogen, optionally substituted lower alkyl,

optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO2, NR5 (Rr> is selected independently from the same substituent group as R'O, "N=and =N~), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted
8

aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle Lower allcyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyli
Ry is hydrogen, halogen, hydroxy, optionally substituted lower allcyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or
Rl is hydrogen or lower allcyl;
R is independently selected from halogen and Substituent group SI>'

Substituent group SI(- optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower allcyl substituted with optionally substituted phosphoric acid residue (wherein the lower allcyl may be intervened with a heteroatom group(s) selected from CO, O, O, S, SO, SOa, NRa (Ra is hydrogen or lower allcyl), -N= and =N0, lower alkoxy lower alkyl, amino lower allcyl optionally substituted with mono- or di- lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di- lower alkyl, optionally substituted lower alkyl sulfonyl amino, halogenated lower alkoxy, hydroxy lower alkyl)
m is an integer of 0 to 3, its pharmaceutically acceptable salt, or solvate thereof.
(13) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein Rx and RH are independently hydrogen or optionally substituted lower.
(14) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein Rx and Ruare hydrogens.
(15) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R3 is hydrogen.
9

(16) A compound according to the above (12), pharmaceutical^ acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.
(17) A compound according to the above (7) or (12), pharmaceutical^ acceptable salt, or solvate thereof, wherein A ring is any one of the following:

(wherein, Il20 to R'10 are each independently a group selected from Substituent group S2, or any two groups of R20 to R'10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R20 and R22), (R23and R2'0, (R25 and R2<0, (R and Rsfy (R-'° and Rs>), (R32 and R3<), (R3s and R^), (R-" and R38), and (R;,9andR'10), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.
Substituent group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl,
10

optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, 0, S, SO, SO2, NR5 (RG is independently selected from the same Substituent group as Rd), -N= and =N0
the stereochemistz'y of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof)

(18) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein R20 to R'10 are each independently hydrogen or substituted lower alkyl, or any two groups of R20 to R'10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3' to 7-membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R2° and R22), (R*» and R2"), (R and R2), (R2' and R2»), (R30 and R31), (R32and R3'1), (R35 and R36), (R37and R33), and (R^andR-'0), taken together with the neighboring atom, may form an optionally substituted 5" to 7- membered carbocyle or optionally substituted 5" to 7- membered heterocycle.
(19) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-I); one of R20 to R2n is optionally substituted lower alkyl and the others are hydrogens.
(20) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A"I)," one of (R20 and R22), (R23 and R2,0, and (R25 and R2G), taken together with the neighboring atom, may form an optionally substituted 5* to 7- membered carbocyle or optionally substituted 5- to 7-membered heterocycle.
(21) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A'I); Z=NR2G, and R23 and R2(J taken together with the neighboring atom may form an optionally substituted 5" to 7-
1.1

membered heterocycle.
(22) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring- is a ring represented by (A-2); one of R27 to R30is optionally substituted lower alkyl and the others are hydrogens.
(23) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A'2); one of (R27and R29) and (R30 and R31), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5" to 7- membered heterocycle.
(24) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); Z=NR31, and R30 and R31 taken together with the neighboring atom may form an optionally substituted 5- to 7-membered heterocycle.
(25) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of R32 to R39 is optionally substituted lower alkyl and the others are hydrogens.
(26) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A"3); one of (R32andR3'0,(R;i5andR;i),(R:i7andR38),and(R;)3andR'o), taken together with the neighboring atom, may form an optionally substituted 5" to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.
(27) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); Z=NR'10, and R;,9and R10 taken together with the neighboring atom may form an optionally substituted 5- to 7' membered heterocycle.
(28) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein Rxis hydrogen; R1'1 is hydrogen or optionally substituted lower.' R3 is hydrogen,' m is 1 to 3 and at least one of Rs is halogen,' A ring is a ring
12

described in Claim 17.
(29) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein Rx is hydrogen,' RH is hydrogen,' R3 is hydrogen; m is 0, or 1 to 3 and at least one of Rs is halogen; A ring is a ring described in Claim 17; R20 to R10 ax*e each independently hydrogen or substituted lower alkyl, or any two groups of R20 to R'10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R20 and R22), (R23 and R*'0, (R25 and R2G), (R27 and R2»), (R3oand R3»), (Ra2and R3'1), (R;ir' and R3), (R and R38), and (R;,9andR'°), taken together with the neighboring carbon atom, may form an optionally substituted 5_ to 7_ membered carbocyle or optionally substituted 5' to 7- membered heterocycle.
(30) A compound of the formula:

(wherein,
D ring is optionally substituted heterocycle;
RI is hydrogen or lower alkyl,'
X is a single bond, a heteroatom group selected from 0, S, SO, SOa and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group,'
R2 is optionally substituted aryl;
R:! is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), pharmaceutically acceptable salt, or solvate thereof
13

(31) A compound selected from the group consisting of'
(3Jff,lla5)-A'-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,II,lla -hexahydro[I,3]oxazolo[3,2-c-?]pyrido[I,2-rf]pyrazine'8-carboxamide;
(4aJ/?,13a-//-[(2)4-Difluorophenyl)methyl]-10-hydroxy-9,II-dioxo-2I3,4a,5,9,II,13,13a •octahydro-li7-pyrido[I,2-a]pyrrolo(r,2':3,4]imidazo[I,2-a']pyrazine-8-carboxamide;

(3aS, 13a6!I-Af{(2,4-Difluorophenyl)methyl]-8-hydroxy-7I9-dioxo-I,2,3,3a,4,5,7,9,].3,13a
•decahydropyridotI'I.DIpyrazinotI-ajpyrrolod-dpyrimidine-IO-carboxamide.'
(4a6,,13ai2)-7V-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9, II-dioxo-2,3,4a,5,9,II, 13,13a
-octahydro-N-pyrido[I,2-a]pyrrolo{II)2':3,4jimidazo[I,2-a']pyrazine-8-carboxamide;
(4a5,,13ai?)-A-[(4-Fluorophenyl)methyl]I0-hydroxy-9,II-dioxo-213,4a,5,9,II,13113a-oct
ahydro-I//;pyrido[II2-a]pyi,rolo[I',2,:3,4]imidazo[I,2-rfjpyrazine"8-carboxamide,'
(SIIa-A-to/I-DifluorophenyOmethyII-e-hydroxy-GJ-dioxo-S-CphenylmethyO.S.S,
7,II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-fI']pyrazine-8-carboxamide;
(3a5,,I3a5)-N-[(4-Fhiorophenyl)methyl]-8-hydroxy-7J9-dioxo-I,2,3,3a,4>5,7,9,13,13a-de
cahydropyridotr'I.OjpyrazinotI-aJpyrrolotI-dpynmidine-IO-carboxamide;
14

(36,,I.Iai?)-//-[(214-Difluorophenyl)methyl]-6-hydroxy-3-[(I5)-I-methylpropyl]-5,7-dioxo
2, 5, 5, 7, 11, 11a .hexahydrotIIoxazoloCS-IpyridoCI-rfIpyi-azine-S-carboxamide,'
(3-S',IIai9-iV-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyI-5I7-dioxo-2I3,5,7,II,IIa
-hexahydro[I,3]oxa7,oIo[3,2-a]pyrido[I,2'rfIpyrazine-8-carboxamide;
(35'IIIai3-A'-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyI-5,7-dioxo-213,517)II)I.Ia-he
xahydro[I,3]oxazolo[312-a]pyrido[I,2']pyrazine-8-carboxamide."
(35,IIai?)-A':[(2,4-Difluoropheny0methyl]-3-(I,I-dimethylethyl)-6-hydroxy-5,7-dioxo-2
.S.S.y.II.IIa-hexahydrofI.SJoxaxoiotS-fIjpyridofI-f/Ipyrazine-S-carboxamide;
(3JIIa/-3-(I,I-Dimethylethyl)-A':[(4-fluorophenyl)methyl]-6-hydroxy-5)7-dioxo-2I3I51
7,II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-f/]pyrazine-8-carboxamide;
(311aJff)-//-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3)5,7,II,IIa
-hexahydi-o[I,3]oxazolo[3,2-a]pyrido[I,2-rfIpyrazine-8-carboxamiide;
(3-S,,IIaJfI!)-A':f(2,4-Difluorophenyl)methyl]-6-hydroxy3-(hydroxymethyl)-5,7-dioxo-2,3,
5,7,II,IIa-hexahydro[I,3]oxazolo[3,2'a]pyrido[II2-rfIpyrazine"8-carboxamide;
(2<5,,3,)-A-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyI-5,7-dioxo-2-phenyl-2,3,5,7
,II,II.a-hexahydro[I,3]oxazolo[3,2-jpyrido[I,2fI']pyrazine-8-carboxamide;
15

(3iUIa6)-7V-[(2,4-DifluorophenyJ)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,
7,II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-fI,]pyrazine-8-carboxamide;
(37?,IIa6)-7-[(214-Difluorophenyl)methyl]-6-hydi-oxy-3-(2-methylpropyl)-5)7-dioxo-2,3)
5,7,.I.I,].].a-hexahydro[j.,3]oxazolo[3,2-]pyrido[I,2'a']pyrazine-8-carboxamide;
(5aT?,14aT2)-A':[(2J4-Difluorophenyl)methylJ-II-hydroxy-10,12-dioxo-I,2,3,4,5a,6,10,12,
14,14a-decahydropyrido[I,2'<3Jpyrido[r,2':3,4]imidazo[I,2-(7']pyrazine'9-carboxamide;
(2r,3J5)-//-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(metb.yloxy)methyl]-5,7-dioxo-2-p
henyl-2,3,5,7, II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-tf]pyrazine-8-carboxamide
(3.5,:LIa/?)-3-(CyclohexylmethyI)-Ar-[(2,4-diflnorophenyl)methylJ-6-hydroxy-5,7-dioxo-2,
3)5,7,II,IIa"hexahydro(I,3]oxazolo[3,2-a]pyrido[I,2-fI']pyrazine-8-cat'boxamide;
(SIIa-TV--DifluorophenyDmethylj-G-hydroxy-S-d-methylethyD-S-dioxo.S,
7,II,IIa-hexahydro[I.,3]oxazolo[3,2-a]pyridoII,2-rf]pyrazine-8-carboxamide;
(5a/?,14a6)-7V;K2,4-Difluorophenyl)methyl]-12-hydi-oxy-II,13-dioxo-5a16a,7,II,13,14a-
hexahydro-5H;indeno[I',2':4,5]fI,3]oxazolo[3/2-a]pyrido[I,2-a']pyrazine-10-carboxamid
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16

(26,,3,IIa6)Ar-[(2,4-Difluoi-ophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2J3,5,7,
II,IIa-hexahydro[I,3]oxazolo[3,2-/3]pyrido[I,2-c(']pyrazine-8-carboxamide;
(2JS,13i?1IIay)-Ar-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,
IIJIIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-(7']pyrazine-8-cai'boxamide;
(3i?,IIa-A[(2,4-Difluorophenyl)meth.yI]-6-hydroxy-3-(I-methylethyl)-5,7-dioxo-2,3,5,
7,II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-fI']pyrazine-8-carboxamide;
(3-S'1IIa/?)-Ar-[(2,4-Difluoroph.enyl)methyl]-6-hydroxy-3-(2-(methylthio)ethyl]-5,7-dioxo-
2,3,I),7,II,IIa-hexahydro[I,3]oxazolo[3,2-a]pyrido[I,2-rf]pyrazine-8-carboxamide."
(3£',IIa/2)-Ar-[(2,4-DiflnorophenyI)methyl]-6-hydroxy-3-f2-(methylsulfonyl)ethyl]-5,7-di
oxo-2,3,5,7,II;IIa-hexahydro[I,3]oxazolo[3,2-.a]pyrido[I,2-a1pyi'azine-8-carboxamide;
(35',IIa/?)-A[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(I//-indol-3-ylmethyl)-5>7-dioxo
.S.S.II.IIa-hexahydrofI.SJoxazolotS-ajpyridotI-dpyi-azine-S-carboxamide,"
(4E, 12a/i!)-A'-K4-fluorophenyl)methyl]-7-hydroxy-4-methyM-(2-methylpropyl)-6,8-diox
o-I,2,3,4,6,8,12,12a-octahydropyrido[I',2':4,5jpyrazino[I,2-a]pyrimidine-9-carboxamid
e;
17

(4i?,12a/i5-N-{(4-FluorophenyI)methyl]-7-hydroxy-4-methyM-(I-methylethyl)-6,8-diox
o-I,2,3,4,6,8,12,12aoct:ahydropyrido[I'I2':4(5]pyrazino(I,2-a]pyrimidine-9-cai-boxamid
e;
(4-5',.1.2a6)-N-((2,4-DifluorophenyI)methylJ-7-hydroxy-4-methyM-(2-methylpropyl)-6,8-
dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[I',2':4,5]pyrazino[I,2-aJpyrimidine-9carboxa
mide."
(412a-I-(CyclopropylmethyI)-iV-[(214-difluorophenyl)methyl]-7-hydroxy-4-methyl-6
,8-dioxo-IJ2,3,4,6,8,12,12a-octahydropyridotI',2':4,5]pyrazino[I,2a]pyrimidine-9-carbo
xamideJ
(46',12a6)-Ar-[(2,4-DifliiorophenyI)methyl]-I-(2-furanylmethyl)-7-hyd roxy4_methyI'6,8
-dioxo-I,2,3,4,6,8>12,12aoctahydropyrido[I',2';4,5jpyrazino[I,2-jpyrimidine-9-carbox
amide,'
(45,12a-5)-A':[(2,4-DifluoI-ophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-I-(I,3fchiazol-
2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydiopyrido[I',2':4,5jpyrazino[I,2 .ajpyrimidine-9c
arboxamide;
(4a/?,6ai?,14a6)-A[(2,4-DifliiorophenyI)methyl]-.12-hydroxy-II,.13-dioxoI,3,4,4a,5,6a,
7,II,13,14a-decahydro-2/f-pyrido[r)2':4,5]pyi-azino[I,2-][3,I]ben2oxa2ine-10-carboxa
mide;
18

(4ai,6ai?,14a5)-N'[(4-FluorophenyI)methyl]-12-hydroxy-II,13-dioxo-I>3,4,4a,5,6a,7,II
,13,14a"decahydro-2jir-pyridoII',2"-4,5]pyrazinoII,2-a3f3,I3benzoxazine-,I0-carboxamicle

;
(3iS,,4ai?,6a5,14a-iV:[(214-Difliiorophenyl)methyl]-12-hydroxy-ll)13-dioxo-3-phenyl-l
13,4,4a,5)6a)7,ll,13,14a-decahydro-2/f-pyrido[r,2,:4,5]pyrazino[l,2-i7][3,l]benzoxazine
-10-carboxamide;
(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-ll,13-d
ioxo-l,2,3,4,4a,5,6,6a,7, ll,13,14a-dodecahydropyrido[r,2':4,5]pyrazino[l12-a]quinazoli
ne-10-carboxamidel
(6aE,7aS,llaS)-N-[(2,4-Difluorophenyl)methyl]-l-hydroxy-2113-dioxo-2,6a,7,7a,8)9,10)
ll.llaS-decahydro-GHpyridofr'.Glpyrazinotl-albenzimidazole-S-carboxamide;
(6aS)7aS,llaS)-N-[(214-Difl\.ioiophenyl)methyl]-l-hydioxy-2,13-dioxo-2,6a,7,7a,8J9,10,
ll,lla,13-decahydro-6H'pyrido[r,2':4,5]pyrazino(l.,2-a]benzimidazole-3-carboxamide;
(5aS,14aS)-N-[(2,4-Difluorophenyl)methylj-11 -hydroxy- 10,12-dioxo-l,2,3,4,5a,6,10,12,
14,14a-decahydropyrido[l,2-a]pyrido[r,2':3,4]imidazo[l,2-d]pyrazine-9-cai-boxamide;
(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydi-oxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,
19

14a-decahydro-lH-pyrido[l12-c]pyridorr,2':4,5jpyrazino[l,2-a]pynmidinG-ll-carboxam
ide;
(4i?,12ay9-iV-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-raethyl-l-(3-methylbutyl)-6,8-d
ioxo-1,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxa
mide;
(45',12a6)-jV:[(2,4-.Difluorophenyl)raethyl]-7-hydroxy-4-methyl-l-(l-methylethyl)-618-di
oxo-l,2,3,4,6,8,12,12a-octahydropyrido[l',2':4,6]pyrazino[l,2-]pyriinidine-9-carboxam
ide;
(45;i2a5)-N-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-l-(3-methylbuty0-6,8-d
ioxo-1,2,3,4,6,8,12,12aoctahydropyrido[l\2M,5]pyrazino[l,2- mide."
(4*5', 12a6)-A':l(2,4-Difluorophenyl)methyl]-7-hydroxy'4-methyl-6,8-dioxo-l-(3-pyridinyl
methyl)-l,2,3,4,6,8,12,12a-octahydropyridolr,2'-'4,5]pyrazino[l,2-a]pyrimidine-9-carbo
xamide,'
(46', 12a-5!)-l-Cyclop ropy 1--1(2,4-difluorophenyl)raethyl.]-7-hydroxy-4-methyl-6,8-dioxo'
l,2,3,4,6,8,12,12a-octahydropyrido(l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide;
(46',12a5!)-7V-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-rnethyM-(2-(methyloxy)ethyl]-
20

6,8-dioxo-l,2,3,4,6,8,12,12a-octahydropyndo[ri2':4,5]pyrazino[l,2-fl]pyrimidine-9'carb
oxamideJ
(3aS,5aS,13aS)-N-[(2,4-Difluoiophenyi)methyl]llhydroxy-5-(2-mefchylpropyl)-10,12-d
ioxo-2,3,3a14)5,5a,6,10,12,13a-decahydro-l.H-cyclopenta[e]pyrido[r,2,:4,5jpyra7,ino[ll2
a]pyrimidine-9-carboxamide;
(3if,Ha)-N-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy5,7-dioxo-2,3,5,7,ll,lla-h
exahydro[l,3]oxazolo[3,2-a]pyndo[l,2-tf)pyrazine'S-carboxamide;
(4aS,6aS,14aS)-N-[(2,4-DifJuorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-
11,13-dioxo-l, 2,3,4,43,5,6,6a,7, .11,13,14a-dodecahydropyrido[l',2':4,5]pyrazino[l,2-a]q
uinazoline-lO-carboxamide,"
(3aR,5aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-ll-hydi-oxy-10,12-dioxo-l,2,3,3a,4,5a,
6,10,12,13a-decahydrocyclopenta[d]pyrido[r,2':4,5]pyrazino[2,l-b][l,3]oxazine-9-carbo
xamidei
(4aS,6aS,14aS)-N-[(2,4-.Difluorophenyl)methyl.]-12-hydroxy-6-methyl-11,13-clioxo-1,2,3
,4,4a,5,6,6a,7,H,13,14a'dodecahydropyrido[r,2':4,5jpyrazinoll,2-a]quinazoline-10-cai'
boxamide;
(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethylJ-ll,
2.1

13-dioxoa,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[l\2':4,5]pyrazino[l,2-a]quin
azoiine-10-carboxamide;
(4aS,6aS,14aS)-6-[2-(Acetylamino)ethyU-N-[(2,4-difluorophenyl)methyl]-12-hydroxyl
l,13-dioxo-l,2,3,4,4a,5,6,6a,7,ll,.1.3,14adodecahydropyrido[l',2':4,5jpyrazino[l,2-a]qui
nazoline- 10-carboxamidei'
(35;.lla7?)-N-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7, ll,lla-h
exahydro[l,3]oxazolo[3,2-a]pyrido[l,2-a"]pyrazine-8-carboxamide;
(36,Illai?)-3-Butyl-A[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,517,ll,lla-h
exahydro[l,3]oxazolo[3,2'ij]pyrido[l,2-rfjpyrazine-8'carboxamide,'
(36;ila/?)-A[(2,4-DifluorophenyJ)methyl.]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-G,7'
dioxo-2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-(7']pyrazine-8-carboxamide
i
(4S,12aS)-l-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyi-6,8-dioxo-l
l2)3,4,6,8112,12a-octahydropyrido(ll,2'--4,5]pyraznio{l,2-a]pyrimidine'9-carboxamidei'
(46,,12a>-At[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-l-(tetrahydro-
2/f-thiopyran-4-yl)'1.2,314J6,8,12)12a-octahydropyrido[l'12,:4,5]pyrazino[lJ2a]pyrimid
ine-9-carboxamide,"
22

(45',12a)-A':[(2,4-Difluorophenyl)methyl]-7-hydroxy-l,4-bis(2-methylpropyl)-6l8-dioxo
-1,2,3,4,6,8,12,12a-octahydropyrido(r,2':4,5]pyrazinotl,2-fl]pyrimidine-9-carboxamide;
(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy6-(2-hydroxyethyl)-ll,13-d
ne_ 10'carboxamide.'
{4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxyll,13-dioxo-
l,2,3,4,4a,5,6;6a,7,11,13,14a-dodecahydropyrido[r,2':4,5]pyrazino[l,2-a]quinazoline-1
O-carboxamide,"
(4aS,6aS,14aS)-N-[(2,4-.Difluorophenyl)methyl]-12-hydroxy-ll,13-dioxo-6-[2-(l-pyrroli
dinyl)ethylJ-.l,2,3]4,4aJ5,6,6a,7,ll,13,14a-dodecahydropyrido[l',2':4,5]pyrazino(l,2a]q
uinazoline- 10-carboxamide;
(4aS)14aS)-N-[(2,4-Difluorophenyl)raethyJ]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,141l
4a-decahydro-lH-pyrido[l,2-c]pyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-ll-cai-boxami
de;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-l-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide;
23

(4S,12aS)-l-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy4-methyl-6,8-dioxo-l,2,3,4,6,8,12,12a-octahydropyriclo[l',2':4,5)pyrazino[l,2-a]pyrimidine-9-carboxamide,'
(4S,12aS)-N-[(4-Fluorophenyl)methylJ-7-hydfoxy-4-methyl-l-(2-methylpropyl)-6,8-dioxo-l.a/e.S..a-octahydropyridotl'Jpyrazinofl-alpyrimidine-O-carboxamide',
(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7'hydroxy-l,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[l\2':4,5]pyrazino[l,2-alpyrimidine-9xarboxamide;
(46',12a/g)-A/'-[(4-Fluorophenyl)methylJ'7-hydroxy-4methyl-6,8-dioxo-l-(tetrahydro-2/7thiopyran-4-yl)-l,2,3,4J6,8,12,12a'octahydropyrido[r,2':4,5]pyrazino[lJ2-Jpyrimidiae•9'carboxamide,'
(45',12a6!)-Ar-K2,4-Difluorophenyl)methyl]-7-hydi-oxy-lJ4-dimethyl-6,8-dioxo-l,2,3,4,6,8,12,12a-octahydi-opyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide;
(45;i2a5)-jV-l(4-Flnorophenyl)methyU-7-hydroxy-4-methyl-l-(l-methylethyl)-6,8-dioxo-l,213,4,6,8,12,12a-octahydropyrido[l',2'.'4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide;
(45;i2al-N-[(4-FluorophGnyl)methyl]-7-hydroxy-l,4-bis(2-methylpropyl)-6,8'dioxo-l,2,3,4,6,8,12,12a-octahydropyado[l',2':4,5]pyrazino[l,2--alpyrimidine-9-cai'boxamide;
24

enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.
(32) A compound selected from the group consisting of-'
(4a6U3a./t')-Ar-f(2,4-Difluorophenyl)methyl]-10-hydroxy-9,il-dioxo-2,3,4a,5)9,ll,13,13a•octahydro-li7-pyrido[l,2-]pyri"olo[l',2':3,4jimidazo[l,2-<3']pyrazine'8'carboxamide;

(4a6,,13ai?)-A[(4-Fluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4a,5,9,H,13,13a-octahydro-l-pyrido[l,2 ,gJpyrrolo[r,2,'-3J4limidazo[l,2-a,]pyrazine-8-carboxamicle;
(36'1llai?)-A[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(liS)-l-methylpropyl]-5,7-dioxo-2,3,5J7,llJllahexahydro(l,3]oxazolo[3,2-]pyrido[],2-Q']pyrazine-8-carboxamide;
(3£',llai?)-A'-l(2;4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2)3,5,7,ll,lla-hexab.ydro[l,3]oxa7.olo[3,2-]pyrido[l,2-rflpyrazine-8-carboxamide;
(351,1la)-A[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,710X0-2,3,5,7,1:1,113-116xahydro[l,3]oxazolo[3,2-Jpyrido[l,2-o']pyrazine-8-cai:boxamide;
(46U2a6)-7V-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-l-(2-methylpropyl)-6,8-dioxo-l,2J3,4,6,8,12,12a-octahydropyriclo[l',2,:4,5]pyrazino[.l,2-a]pyrimidine-9-carboxa
25

mide;
US, 12a6)-l-(Cyclopropylmethyl)-A':[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-l,2,3,4,6,8, .a-octahydropyridotr'.Slpyrazinotl-dpyrimidine-Q-carboxamide;
(4ai?,6a7?,14a6)-A[(214-Difluorophenyl)methyl]-12-hyclroxy-lll13-dioxo- 1,3,4,4a, 5,6a,7,11,13,14a-decahydro-2i/'-pyrido[r,2,-'4,5]pyrazino[l,2-a] [3, ljbenzoxazine- 10-carboxamide>"
(4a/2,6a,14a-A[(4-Fluorophenyl)methyl]-12-hydroxy-ll,13-dioxo-l,3,4,4a,5,6a,7,ll, 13,14a-decahydro-2/fpyrido[l', 2' :4,5jpyrazino[l, 2" a] [3, ljbenzoxazine" 10 -carboxamide
4S,9aR)-5-Hydroxy4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-l-oxa-4a,8a-diaza anthracene-7 car boxy lie acid 2,4,-difluorobenylamide;
4R19aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a>10hexahydro-2H-l-oxa-4a,8a-diaza anthracene-7'carboxylie acid 2,4,-difluoro-benylamide;
2R,9aS)-5-Hydroxy-2methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benylamide;
26

enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof,' mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.
(33) A compound according to the above (31) or (32) wherein the pharmaceutically acceptable salt is a sodium salt.
(34) A pharmaceutical composition comprising a compound according to any one of the above (l) to (33), or a pharmaceutically acceptable salt, or solvate thereof.
(35) A pharmaceutical composition according to the above (34), which is an antivHIV agent.
(36) A process for the preparation of a compound of formula (I-20a)

wherein Re is one or two halogen,' Rz is Ci-salkyl, CGuarylCi-aalkyl, Cc-Maryl, or alkoxy; and Pl is Ce-MarylCi-salkyl;
comprising condensing a compound of the formula

wherein Re is one or two halogen,' Rr,° is Ci-salkyL' and P1 is Cc-narylCi-salkyl;
27

with a compound of the formula

wherein Rz is Ci-salkyl, Cf,uarylCi isalkyl, Cc-i-iaryl, or alkoxy;
to form a compound of formula (I-20a).
(37) A process for the preparation of a compound of formula (I-20b)

wherein Rc is one or two halogen! R* is Ci-aalkyl, Cci-iarylCi-aalkyl, Cc-i.iaryl, or alkoxy; and P1 is Cei-iarylCi-aalkyl,'
comprising condensing a compound of the formula

wherein Rc is one or two halogen.' Rso is Ci-salkyl; and P1 is CG-i-iarylCi-aalkyl.'
with a compound of the formula

wherein Rz is Ci-salkyl, Cfi-uarylCi-aalkyl, Cc-i.iaryl, or alkoxy.'
to form a compound of formula (I-20b).
28

(38) A process for the preparation of a compound of formula (1-2 la)

wherein R° is one or two halogen; and P1 is Co-HarylCi-salkyL'
comprising condensing a compound of the formula

wherein R° is one or two halogen," R50 is Ci-salkyL' and P1 is Cci with a compound of the formula

to form a compound of formula (1-2la).
(39) A process for the preparation of a compound of formula (1-2lb)

wherein Re is one or two halogen.' and P1 is Cfii.iarylCi-salkyl;
29

comprising condensing a compound of the formula

wherein R° is one or two halogen," R5() is Ci-aalkyL' and P1 is CeuarylCifialkyl;
with a compound of the formula

to form a compound of formula (I-21b).
(40) A process for the preparation of a compound of formula (I"22a)

wherein Re is one or two halogen; and P1 is Cfii.iarylCi-aalkyl,'
comprising condensing a compound of the formula

wherein Rc is one or two halogen,' Rn0 is Ci-aalkyl; and P1 is Co-MarylCi-aallcyl.'
with a compound of the formula
30

to form a compound of formula (I"22a).
(41) A process for the preparation of a compound of formula (I22b)

wherein Re is one or two halogen.' and P1 is CfiuarylCi-salkyl;
comprising condensing a compound of the formula

wherein R° is one or two halogen; Rso is Ci-aalkyl; and P1 is CijuarylCi-salkyl;
with a compound of the formula

to form a compound of formula (I'22b).
(42) A process for the preparation of a compound of formula (123a)

wherein Re is one or two halogen,' and PI is CG-uarylCi-aalkyl;
3.1

comprising condensing a compound of the formula

wherein Re is one or two halogen,' R50 is Cisalkyl." and PI is Ca uarylCi-aalkyl;
with a compound of the formula

to form a compound of formula (I-23a).
(43) A process for the preparation of a compound of formula (123b)

wherein Rv is one or two halogen; and P1 is Cc-uarylCi-salkyL"
comprising condensing a compound of the formula

wherein R° is one or two halogen; R50 is Ciaalkyl;
with a compound of the formula
32

to form a compound of formula (I"23b).
(44) A process for the preparation of a compound of formula (I'24a)

wherein R° is one or two halogen! II" is Ci-salkyl; Rzl is hydrogen, Ca-Gcycloalkyl, ,
heterocycle, or Ci-salkyl optionally substituted with hydroxy, Ca-ccycloalkyl, alkoxy,
heterocycle, heteroai'yl, Co-naryl, or amino, wherein said amino may be optionally
substituted with-C(0)Ci-aalkyl or Ci-salkyl; and P1 is Cc-uarylCi-salkyl."
comprising condensing a compound of the formula

wherein Re is one or two halogen; and R50 is Ci-salkyl; and P1 is Cfi-narylCi-salkyl;
with a compound of the formula

wherein R* is Ci-salkyl; Rzl is hydrogen, Ca-ocycloalkyl, , heterocycle, or Ciaalkyl
optionally substituted with hydroxy, C;i ocycloalkyl, alkoxy, heterocycle, heteroaryl,
Cs-uaryl, or amino, wherein said amino may be optionally substituted with
-C(0)Cj-8alkyl or Ci-salkyl;
33

to form a compound of the formula (I"24a).
(45) A process for the preparation of a compound of formula (I-24b)

wherein RG is one or two halogen,' Rz is Ci-salkyl.' R*1 is hydrogen, C;)-6cycloalkyl, , heterocycle, or Ci aalkyl optionally substituted with hydroxy, Ca-ccycloalkyl, alkoxy, heterocycle, heteroaryl, Couaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-aalkyh" and P1 is Cc-MarylCt-aalkyL" comprising condensing a compound of the formula

wherein Rc is one or two halogen; RD0 is Ci-salkyl; and P1 is Cc-uarylCi-aalkyl; with a compound of the formula

wherein Rz is Ci-salkyL' and RzI is hydrogen, Cu-ecycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, Ca-ccycloalkyl, alkoxy, heterocycle, heteroaryl, Cc-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-aalkyl;
to form a compound of the formula (I'24b).
34

(46) A process for the preparation of a racemic compound of formula (1-25)

wherein Re is one or two halogen.' RzI is hydrogen, Ca-ccycloalkyl, , heterocycle, or Ci-aalkyl optionally substituted with hydroxy, Cn-r;cycloalkyl, alkoxy, heterocycle, heteroaryl, CG-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ct-8alkyl or Ci-salkyl.' and P1 is is Cci-iarylCi-salkyl;
comprising condensing a compound of the formula

wherein Re is one or two halogen! and R50 is CiaalkyL' and P1 is Ce-uarylCi-salkyl." with a racemic compound of the formula

wherein RKl is hydrogen, CyfjcycLoalkyl, , heterocycle, or Ci-aalkyl optionally substituted with hydroxy, C3-Gcycloalkyl, alkoxy, heterocycle, heteroaryl, Cuuaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-»alkyl or Ci-salkyl;
to form a racemic compound of the formula (1-26).
(47) A process for the preparation of a racemic compound of formula (126)
35

wherein Rc is one or two halogen,' R7-1 is hydrogen, Cn-Gcycloalkyl, , heteroeycle, or Cisalkyl optionally substituted with hydroxy, Ciiccycloalkyl, alkoxy, heteroeycle, heteroaryl, Co-i-iaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-aalkyi or Ci-galkyl; and P1 is Cc-MarylCi salkyl;
comprising- condensing a compound of the formula

wherein Ru is one or two halogen.' RM is Ci-galkyl; and P1 is Cc HarylCi-salkyl; with a racemic compound of the formula

wherein R*1 is hydrogen, Ca-ccycloalkyl, , heteroeycle, or Ci-salkyl optionally substituted with hydroxy, Ca-Gcycloalkyl, alkoxy, heteroeycle, heteroaryl, CG-uaryl, or amino, wherein said amino may be optionally substituted with - C(0)Ci-8alkyl or Ciaalkyl;
to form a racemic compound of formula (P26).
(48) A process for the preparation of a racemic compound of formula (I"27)

wherein R° is halogen! and P1 is CcuarylCi-salkyl;
comprising condensing a compound of the formula

wherein R° is one or two halogen; R50 is CiaalkyL* and P1 is Coi.iarylCi aalkyl; with a racemic compound of the formula

to form a racemic compound of formula (1-27).
(49). A compound of formula (I"20a) described in above (36). formula (I-20b) described in above (37), formula (I"21a) described in above (38), formula (I'21b) described in above (39), formula (I"22a) described in above (40), formula (I'22b) described in above (41), formula (I"23a) described in above (42), formula (123b) described in above (43), formula (I"24a) described in above (44), formula (I"24b) described in above (45), formula (125) described in above (46), formula (1-26) described in above (47), or formula (1-27) described in above (48), or a pharmaceutical acceptable salt thereof.
(50) A compound of formula (I"20a) described in above (36). formula (I"20b) described in above (37), formula Q-21a) described in above (38), formula (1-2 Ib) described in above (39), formula (I22a) described in above (40), formula (P22b) described in above (41), formula (I-23a) described in above (42), formula (P23b)
37

described in above (43), formula (L24a) described in above (44), formula (I"24b) described in above (45), formula (1-25) described in above (46), formula (1-26) described in above (47), or formula (1-27) described in above (48), or a pharmaceutically acceptable salt thereof, wherein each P1 is hydrogen.
The present invention further provides a pharmaceutical composition containing any of the compounds shown above, a pharmaceutically acceptable salt or a solvate thereof, especially an anti-HIV agent.
[Effect of the Invention]

[Effect of the Invention]

[0005]
The present invention compounds possess an integrase inhibitory activity and/or a cell-growth inhibitory activity against virus, especially HIV. Accordingly, they are useful for the prevention or treatment of various diseases mediated by integrase or virus infection diseases (e.g., AIDS). The present invention further provides a process for preparing a diastereomer, a mixture thereof, or racemate.
(Preferred Embodiment of the Invention]
[0006]
The terms used herein are explained below. Each term, alone or in combination with another tern, means as follows.
"Lower alleylene" means a straight or branched Cl to C6 alkylene such as methylene, ethylene, trimethylene, n-propylene, tetramethylene, ethylethylene, pentamethylene, or hexamethylene, preferably Cl to C4 straight alkylene such as. methylene, ethylene, trimethylene, and tetramethylene, more preferably methylene or ethylene.
"Lower alkenylene" means a straight or branched C2 to C6 alkenylene, which consists of the above "Lower alkylene" having one or more double bonds, such as vinylene, propylene, or butenylene, preferably a straight C2 to C3 alkenylene such as vinylene or propylene.
"Lower alkyl" means a straight or branched Cl to ClO alkyl such as methyl, ethyl, n-propyl, i-propyl, t-butyl, isobutyl, sec-butyl, n-pentyl, and n-hexyl, and preferred is Cl to C3 alkyl, more preferred is methyl, ethyl or n-propyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, and n-desyl, preferably Cl to C6 lower alkyl, more preferably Cl to C4 lower alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, and isohexyl.
38

When lower alkyl is intervened with "-N=" or "=N-", the lower alkyl may have a double bond to form -CH2-N=CH2, -CH=N-CH3etc.
"Alkenyl" means a straight or branched C2 to C8 alkenyl, which consists of the above "alkyl" having- one or more double bonds, such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, and 3methyl-2butenyl, preferably C2 to C6 alkenyl, and more preferably C2 to C4 alkenyl.
"Lower alkenyloxy" means oxy attached to the above lower alkenyl, such as vinyloxy, l-propenyloxy, 2-propenyloxy, l'butenyloxy, 2-butenyloxy, 3-butenyloxy, 1,3'butadienyloxy, and 3-methyl-2butenyloxy.
"Cycloalkyl" means C3 to C8 cyclic saturated hydrocarbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, and cyclooctyl, preferably C3 to C6 cycloalkyl.
"Cycloalkyl lower alkyl" means lower alkyl substituted with the above cycloalkyl, such as cyclopropylmethyl, cyclop ropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and cyclohexylethyl, and preferably C3 to C6 cycloalkyl lower alkyl.
"Aryl" means monocyclic aromatic hydrocarbon (e.g\, phenyl) and polycyclic hydrocarbon (e.g., l-naphthyl,2- naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-phenanthryl, 3'phenanthryl, 4-phenanthryl, 9-phenanthryl), preferably phenyl or naphthyl (e.g., l-napthyl, 2-naphthyl).
"Aralkyl" or "aryl lower alkyl" means the above lower alkyl substituted with 1 to 3 of the above aryl, such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, 1-napthylmethyl, 2- napthylmethyl, preferably benzyl.
"Aryloxy" means oxy attached to the above aryl, such as 1-naphthyloxy, 2-naphthyloxy, 1-anthryloxy, 2-anthryloxy, 9-anthryloxy, 1-phenanthryloxy, 2-phenanthryloxy, 3phenanthryloxy, 4-phenanthryloxy, and 9-phenanthryloxy, preferably phenyloxy or naphthyloxy (e.g., 1" napthyloxy, 2-naphthyloxy).
"Heterocyclic group" means "heteroring" or "heteroaryl".
"Heteroring" means a non-aromatic ring which has at least one of N, 0 and/or S in the ring and may be bonded at any substitutable position, preferably 5" to

7-membered ring, such as 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, l-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-imidazolyl, 2-imidazolyl, 4-imida7,olyl, 1-imidazolidinyl, 2-imidazolidinyl, 4'imidazolidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 1-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperadinyl, 2-piperadinyl, 2-morpholinyl, 3-morpholinyl, morpholino, and tetrahydropyrauyl. The non-aromatic ring is a
39

saturated or unsaturated ring.
"Heteroaryl" means monocyclic aromatic hetero-type ring- or condensed aromatic hetero-type ring.
"Monocyclic aromatic hetero-type ring" means a 5- to 8- membered aromatic ring, which contains 1 to 4 of 0, S, P and/ or N and may be bonded at any substitutable position.
"Condensed aromatic hetero-type ring" means a group wherein an aromatic ring containing 1 to 4 of O, S, P and/ or N is condensed with 1 to 4 of 5- to 8membered aromatic ring(s) or the other 5- to 8-membered aromatic heteroring(s).
Examples of "heteroaryl" include furyl (e.g., 2-furyl, 3'furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrrolyl (e.g., lpyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazole-l-yl, l,2,4-triazole-3"yl, l,2,4-triazole-4-yl), tetrazolyl (e.g., rtetrazolyl, 2-tetrazoiyl, 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5'oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyO, thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazoiyl), pyridil(e.g., 2-pyridil, 3-pyridii, 4-pyridil), pyridazinyl (e.g., 3pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidiny, 5-pyrimidinyl), furazanyl (e.g., 3-furazanyl), pyrazinyl (e.g., 2-pyrazinyl), oxadiazolyl (e.g., l,3,4oxadiazole-2-yl), benzofuryl (e.g., 2-benzo[b.]furyl

2-pyrazinyl), oxadiazolyl (e.g., 1,3,4oxadiazole-2-yl), benzofuryl (e.g., 2-benzo[b.furyl, 3-benzo[bJfuryl, 4-benzo[b]furyl, 5-benzofbJfuryl, 6-benzo(bJfuryl, 7-benzofb]furyl), benzothienyKe.g., 2-benzo[bJthienyl, 3*benzo(bJthienyl, 4-benzo[b]thienyl, 5-benzofb|thienyl, 6-benzofbjthienyl, 7-benzofbithienyl), benzoimidazolyl (e.g., J.-benzoimidazolyl, 2-benzoimidazolyl, 4-benzoimidazolyl, 5-benzoimidazolyl), dibenzofuryl, benzooxazolyl, quinoxalinyl (e.g., 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl), quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl), quinolyl(e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8quinolyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), isoquinolyl (e.g., 1-isoquinolyl, 3'isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), pnrinyl, pteridinyl (e.g., 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl), carbazolyl, phenanthridinyl, acridinyl (e.g., 1-acridinyl, 2-acridinyl, 3-acridiny3, 4-acridinyl, 9- acridinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5'indolyl, 6'indolyl, 7-indolyl), isoindolyl, phenandinyl (e.g., 1- phenandinyl,
40

2- phenandinyl) or phenothiadinyl (e.g., 1- phenothiadinyl, 2-phenothiadinyl, 3-phenothiadinyl, 4-phenothiadinyl).
"Heterocycle" means a cycle which can be lead to the above heterocyclic group.
"Heterocyclic group lower alkyl" or "Heterocycle lower alkyl" means lower alkyl substituted with the above heterocyclic group.
"Heterocyclic group oxy" or "Heterocycle oxy" means an oxy attached to the above heterocyclic group.
"Heterocyclic group carbonyl" or "Heterocyclecarbonyl" means a carbonyl attached to the above heterocyclic group
"Lower alkoxy" or "alkoxy" means an oxy attached to the above lower alkyl, such as methoxy, ethoxy, n"propoxy, isopropoxy, n'butoxy, isobutoxy, tert'butoxy.
"Lower alkylcarbonyl", "cycloalkylcarbonyl", "cycloalkyl lower alkylcarbonyl", "lower alkoxycarbonyl", "arylcarbonyl", "aryl lower alkylcarbonyl", "aryloxycarbonyl", "heterocyclecarbonyl", "heterocycle lower alkylcarbonyl", and "heterocycle oxycarbonyl", each means a carbonyl attached to the above "lower alkyl", "cycloalkyl", "cycloalkyl lower alkyl", "lower alkoxy", "aryl", "aryl lower alkyl", "aryloxy", "heterocycle", "heterocycle lower alkyl", and "heterocycleoxy", respectively.
[0007]
When a substituent(s) is/are present on "optionally substituted lower alkyl", "optionally substituted cycloalkyl", "optionally substituted cycloalkyl lower alkyl", "optionally substituted lower alkenyl", "optionally substituted lower alkoxy", "optionally substituted aryl", "optionally substituted aryl lower alkyl", "optionally substituted aryloxy", "optionally substituted aryloxy lower alkyl", "optionally substituted heterocyle, "optionally substituted heterocyclic group", "optionally substituted heterocycle lower alkyl", "optionally substituted heterocycleoxy", "optionally substituted lower alkenyloxy", "optionally substituted lower alkylcarbonyl", "optionally substituted cycloalkylcarbonyl", "optionally substituted cycloalkyl lower alkylcarbonyl", "optionally substituted lower alkoxycarbonyl", "optionally substituted arylcarbonyl", "optionally substituted aryl lower alkylcarbonyl", "optionally substituted aryloxycarbonyl", "optionally substituted heterocyclecarbonyl", "optionally substituted heterocycle lower alkylcarbonyl", "optionally substituted heterocycleoxycarbonyl", "optionally substituted lower alkylene", "optionally substituted lower alkenylene", "optionally substituted phosphoric acid residue", "optionally substituted carbocycle" or "optionally
41

substituted heterocycle", each may be substituted with the same or different, 1 to 4 group(s) selected from Substituent group B at any position.
Examples of Substituent group B include hydroxy, carboxy, halogen (F,Cl,Br,I), halo lower alkyl (e.g., CFa.CHaCFa, CH-iCCl.d, halo lower alkoxy (e.g., OCF3, OCHaCl, OCHaCClu), lower alkyl (e.g., methyl, ehtyl, isopropyl, tertbutyl), lower alkenyl (e.g., vinyl), lower alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy, butoxjO, lower alkenyloxy (e.g., vinyloxy, allyloxy), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t.ert.-butoxycarbonyl), nitro, nitroso, optionally substituted amino (e.g., alkylamino (e.g., methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, trithylamino), hydroxyamino), azido, aryl (e.g., phenyl), aralkyl (e.g., benzyl), cyano, isocyano, isocyanate, thiocyanate, isothiocyanate, mercapt, alkylthio (e.g., methylthio), alkylsulfonyl (e.g., methansulfonyl, ethansulfonyl), optionally substituted alkylsulfonylamino (e.g., methanesulfonylamino, ethansulfonylamino, N-methyls ulfony FN'-methylamino), optionally substituted carbamoyl (e.g., alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl)), sulfamoyl, acyl (e.g., formyl, acetyl), formyloxy, haloformyl, oxal, thioformyl, thiocarboxy, dithiocaiboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazine azido, ureido, amiziuo, quanidino, phthalimide, oxo, phosplioric acid residue, lower alkyl which is substituted with a phosphoric acid residue and may be intervened with a heteroatom group(s), aryl substituted with a phosphoric acid residue, aralkyl substituted with a phosphoric acid residue, lvydroxyl lower alkyl, preferably hydroxy, carboxy, halogen(F,Cl,Br,I), halo lower alkyl (e.g., CFCrCFa, CH2CCl3), halo lower alkoxy (e.g., OCF;), OCHvCF:i, OCH2CCl3), lower alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy), optionally substituted amino (e.g., alkylamino (e.g., methylamino, ethylamino, dimethylamino), oxo, or phosphoric acid residue.
Examples of a substituent of "optionally substituted amino" or "optionally substituted carbamoyl" include mono- or di" lower alkyl, lower alkylcarbonyl, lower alkylsulfonyl, optionally substituted lower alkyl (e.g., methyl, ethyl, isopropyl, benzyl, cai'bamoylalkyl (e.g., carbamoylmethyl), mono' or di- lower alkylcarbamoyl lower

alkyl (e.g., dimethylcarbamoylethyl), hydroxyl lower alkyl, heterocycle lower alkyl (e.g., morpholinoethyl, tetrahydropyranylethyl), alkoxycarbonyl lower alkyl (e.g., ethoxycarbonylmethyl, ethoxycarbonylethyl), mono' or di- lower alkylamino lower alkyl (e.g., dimethylaminoethyl)), lower alkoxy lower alkyl (e.g., methoxyethyl,
42

ethoxymethyl, ethoxyethyl, isopropoxyethyl), acyl (e.g., formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butylyl, isobutylyl, valeryl, isovaleryl, pivaroyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, ethoxycarbonylmethylcarbonyl), lower alkoxy lower alkylcarbonyl (e.g., methoxyethylcarbonyl), lower alkylcarbamoyl lower alkylcarbonyl (e.g., methylcarbamoylehtylcarbonyl), alkoxycarbonylacetyl), optionally substituted arylcarbonyl (e.g., benzoyl, toloyl), optionally substituted aralkyl (e.g., benzyl, 4-fluorobenzyl), hydi'oxy, optionally substituted lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, isopropylsulfonyl, 2,2,2-trifluoroethanesulfonyl, benzylsulfonyl, methoxyethylstilfonyl), lower alkyl, or arylsulfonyl optionally substituted with halogen (e.g., benzenesulfonyl, tohienesulfonyl, 4-fluorobenzenesulfonyl, fluorobenzenesulfonyl), cycloalkyl (e.g., cyclopropyl), aryl optionally substituted with lower alkyl (e.g., phenyl, trithyl), lower alkylaminosulfonyl (e.g., methylaminosulfonyl, dimethylaminosulfonyl), lower alkylaminocarbonyl (e.g., dimethylaminocarbonyl), lower alkoxycarbonyl (e.g., ethoxyearbonyl), cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclohexylcarbonyl), optionally substituted sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, dimethylsulfamoyl), lower alkylcarbonylamino (e.g., methylcarbonylamino), heterocycle (e.g., morpholino, tetrahydropyranyl), optionally substituted amino (e.g., mono- or di'alkylamino (e.g., dimethylaraino), formylamino).
As to amino of "optionally substituted amino", "optionally substituted carbamoyl", or "optionally substituted carbamoylcarbonyl", two substituents on the amino together with the neighboring N atom may form an N-containing heterocycle which optionally contains S and/or 0 in the ring (preferably 5" to 7- membered ring or saturated ring) and is optionally substituted with oxo or hydroxy. The optional S atom in the ring may be substituted with oxo. The N-containing heterocycle is preferably a 5- or 6-membered ring such as piperadinyl, piperidino, morpholino, pyrrolidine 2-oxopiperidino, 2-oxopyrrolidino, 4-hydroxymorpholino.
"Phosphoric acid residue" means a group shown of the formula -PCKOH)?.
"Optionally substituted phosphoric acid residue" means a phosphoric acid residue wherein the OH part and/or a hydrogen of the OH is optionally substituted with a phosphoric acid residue, preferably shown by the formula:
43

(wherein, RA and R]i each is independently ORcor NRDRE (wherein Rc, R" and RKare each independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic group, or RD and R]i taken together with the neighboring N atom may form an optionally substituted heterocycle (preferably 5- to 6" membered ring)) or RA and R13 taken together with the neighboring P atom may form an optionally substituted heterocycle (preferably 5" to 6- membered ring)).
Preferably, RA and RiJ are bothORc, or one of them is ORcand the other is NRDR15. Rc, RD and RE each is preferably, independently, lower alkyl (e.g., methyl, ethyl).
The optionally substituted heterocycle formed by RA and R13 taken together with the neighboring P atom may be the following structure:

(wherein, the broken line means a part of the ring)
Hydroxy substituted with optionally substituted phosphoric acid residue is preferably hydroxy substituted with a phosphoric acid residue substituted with di lower alkyls, and more preferably a group of the formula:

Amino substituted with optionally substituted phosphoric acid residue is preferably amino substituted with a phosphoric acid residue substituted with di lower
44

alkyls, and more preferably a group of the formula'
[0008]
(More preferable embodiments)
II1 is hydrogen or lower alkyl, preferably hydrogen.
X is a single bond, a heteroatom group selected from O, S, SO, SO2 and NH (hereafter also referred to as "M"), or lower alkylene or lower alkenylene each may be intervened by the heteroatom. The term of'intervened by" means the following cases-'
1) The heteroatom group is present between carbon atoms which constitutes the alkylene or alkenylene.
2) The heteroatom group is attached to the N atom of the carbamoyl group neighboring to X.
3) The heteroatom group is attached to II2 neighboring to X.
The heteroatom group (M) may be the same or different, and one or more atoms. Examples of that lower alkylene is intervened by a heteroatom group include -M-CH2-, -CH2-M-CH2-, -CHs-M-, and -CH2-M-M-CH2-.
X is preferably a spacer consisting 1 to 3 joined atoms. X is more preferably lower alkylene or lower alkenylene each may be intervened by a heteroatom group, or O. X is most preferably Cl to C3 alkylene, C2 to C3 alkenylene, or 0. Especially preferred is methylene or 0.
R2 is optionally substituted aryl, preferably phenyl. A substituent on the aryl is

the same or different, 1 to 3, preferably 1 to 2 substituent(s), including preferably halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, and lower alkylcarbamoyl, and Substituent group S.I(: optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substitutedphosphoric acid residue, hydroxyl substituted with optionally substitutedphosphoric acid residue, amino substituted with optionally
45

substitutedphosphoric acid residue, lower alkyl substituted with optionally substitutedpbosphoric acid residue (said lower alkyl may be intervened with a hetero atom group(s) selected from 0, S, SO, SO2, NR5 (R5 is independently selected from the same substituent group for R'O, -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally substituted with mono- or di-lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di-lower alkyl, optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, hydroxyl lower alkyl), more preferably halogen,hydroxy,amino,cyano,lower alkyl, lower alkoxy or Substituent group Si, and most preferred is halogen (e.g., F) and/or a group selected from Substituent group SI. A substituent on the aryl is preferably at the 4-position. ,R2 is more preferably phenyl or phenyl substituted with at least halogen, and most preferably 4-halogenophenyl (e.g., 4-F-phenyl). In another embodiment, R2 is preferably phenyl optionally substituted with 1 to 3 R(s) mentioned below.
In all compounds of the present invention, the structure of "-X-R2" is preferably shown by the formula below:

Reach is independently a group selected from halogen and Substituent group SI. Substituent group Si: optionally substituted phosphoric acid residue, aiyl substiUited with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxyl substituted with optionally substituted phosphoric acid residue, amino substituted with optionally

substituted phosphoric acid residue, lower alkyl substituted with optionally substituted phosphoric acid residue (said lower alkyl may be intervened by a heteroatom group(s) selected from CO, O, S, SO, SO2, NR11 (Ra is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, optionally substituted amino lower alkyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), halogenated lower alkyl, lower alkoxy, optionally substituted carbamoyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, and hydroxyl lower alkyl.
46

m is an integer of 0 to 3, preferably 0 or 1 to 2. when m is 1, R is preferably halogen. When m is 2, R is more preferably the same or different group selected from halogen, lower alkyl, lower alkoxy, lower alkoxylower alkyl, halogenated lower alkyl, halogenated lower alkoxy, lower alkylsulfonylamino, carbamoyl, and lower alkylcarbamoyl. More preferably, R is two halogens, or halogen and another group. R preferably locates at the 4-position and optional another position of the benzene ring.
R3can be a various substituent which does not bring a negative effect to the pharmacological activity, including hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy, and optionally substituted amino. Examples of substituent of "optionally substituted" include halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, lower alkylcarbamoyl, aryl, heterocyclic group, lower alkylcarbonyl, lower alkylcarbonyloxy, lower alkoxycarbonyl, halogenated lower alkyl, halogenated lower alkoxy, and preferably halogen, hydroxy, amino, lower alkylamino, lower alkyl, and lower alkoxy. Ra is more preferably hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino, and most preferably hydrogen or lower alkyl (e.g., methyl), esp. hydrogen.
Z2shows C, CH, optionally substituted lower alkylene, lower alkenylene etc., and Z2 and R'1 of Z1 taken together form a ring, whereby compound (I) shows a tricyclic compound (I-I) or (I'II) shown below, or its derivative, tetracyclic compound.

A ring is optionally substituted heterocycle containing at least an N atom. The
47

heterocycle is a 5- to 7-membered ring which contains preferably 1 to 3, more preferably 2 to 3 atoms of 0, S and/or N. The heterocycle is preferably selected from the above heterocycle. The arc optionally contains 1 to 2 heteroatom(s) at any possible position. One of preferable embodiments of A ring is an optionally substituted ring shown below.

(Z is CH2, O, S, SO, SOa or NRi'O
A ring is preferably a ring of (a), (b), or (c).
Z is preferably O or NR»-i.
When Z is NR1 lower alkyl (the substituent is e.g., amino optionally substituted with mono- or di-lower alkyl; cycloalkyl; hydroxy; optionally substituted heterocyclic group (preferably 5- to 7-membered ring, e.g., furyl, thienyl, thiazolyl, pyridil, morpholino, imidazole; examples of the substituent include lower alkyl, halogen); optionally substituted heterocyclecarbonyl (the heterocycle is preferably 5- to 7-membered ring, e.g., morpholinocarbonyl); optionally substituted phenyl (the substituent is e.g., lower alkyl, amino, lower alkylamino, hydroxy, halogen, halogenated lower alkyl, lower alkoxy, halogenated lower alkoxy, lower alkylthio, lower alkylsulfonyl), acetylamino,

carbamoyl, carbamoyl substituted with mono- or di- lower alkyl, lower
48

alkylsulfonylamino, lower alkoxy, carbonyl, halogen, thiol, lower alkylthio), 3) lower alkenyl, 4) acyl (e.g., lower alkylcarbonyl), 5) lower alkylsulfonyl. R19 may be selected from Substituent group S2 shown below.
The other substituent on A ring may be selected from R15 to R18 or Substituent group S2, preferably lower alkyl. Substituents on A ring may form a condensed ring or a spiro ring' as mentioned below, whereby compound (I) includes a tetracyclic compound.
A ring is more preferably any of the following rings:

(wherein, R20 to R'10 are each independently a group selected from Substituent group S2, or any two groups of R20 to R'"1, which bonds to the same carbon atom, taken together with the carbon atom, may form a spiro ring, i.e., an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R20 and R22), (R"and R2'1), (R23and R2<0, (R"and R29), (Il30 and R31), (R32 and R3"), (R35 and R3<0, (R37 and R38), and (R3f,andR40), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.
Substitution group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aiyl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl,
49

optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, 0, S, SO, SO2, NR5 (R5 is independently selected from the same substitution group as R'1), "N= and =N-)
The stereochemistry of an asymmetric carbon represented by * shows the R' or S-configuration, or a mixture thereof)
In one embodiment, R20 to R'10 each is preferably hydrogen, optionally substituted lower alkyl (examples of the substituent: OH, lower alkoxy, cycloalkyl, lower alkylthio, lower alkylsulfonyl, heterocyclic group, aryl, optionally substituted amino (examples of the substituent: lower alkyl, acyl)), cycloalkyl, optionally substituted aryl (examples of the substituent: OH, lower alkyl), and optionally substituted heterocyclic group.
In one embodiment, R2" to R25, R27 to R30, and R32 to R39, each is preferably hydrogen, C1-C8 alkyl, CGC14 aryl C1C8 alkyl, C6-C14 aryl, or alkoxy.
In one embodiment, R26', Rai, and R'10, each is preferably hydrogen, C3~6 cycloalkyl, heterocycle, or C1.-8 alkyl optionally substituted with hydroxy, C3-6 cycloalkyl, alkoxy, heterocycle, heteroaryl, C6_14 aryl, or amino, wherein said amino may be optionally substituted with -C(0)Cl-8 alkyl or Cl-8 alkyl.
More Preferred embodiments are shown below for example
I) When A ring is A'I, preferred is that I) Z is NR2G and R2C and R2'1 taken together form heterocycle, and the others are hydrogens; 2) Z is O or NR2fi, (R20 and R22) or
50

(R'i:i and R21) taken together form cycloalkyl which is substituted with phenyl, the others are hydrogens or optionally substituted lower alkyl.
II) When A ring is A-2, preferred is that I) Z is O, R27 or R28 is lower alkyl, and the others are hydrogens.' 2) Z is NR;!) and R30 and R3> taken together form heterocycle and the others are hydrogens, or It27 and R29 taken together form cycloalkyl and the others are hydrogens ; 3) Z is 0, R27 and It29 taken together form cycloalkyl which may be condensed with phenyl, and the others are hydrogens
R1'1 and Rxare each independently hydrogen, optionally substitutedlower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino,optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy optionally substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened

with a heterotom group(s) selected from O, S, SO, SO2, NRa (R» is hydrogen or lower alkyj), -N= and =N-).
RH and Rx are each independently, preferably, hydrogen, hydroxy], optionally substituted lower alkyl (the substituent is preferably, e.g., amino, lower alkyl amino, hydroxy, lower alkoxy). RH and Rx are preferably hydrogens.
A broken line in the compound (1*1) represents the presence or absence of a bond,
51

provided that when the broken line represents the presence of a bond, Rxis not present.
[0009]
The compound (I) includes the following compounds.

F ring means the same heterocycle as A ring-, preferably 5- to 7-membered ring, and the substituents on F ring are the same as those for A ring. The other symbols are as defined above.
52

(wherein each symbol is as defined above.' Z is O or NR1D; R1S to R,!) are each independently hydrogen or a group selected from the above Substituent group S2, or each combination of (Il15 and Rie), (R'and Ris), (Riand RIS), and (Ri8and Rm) taken together with the neighboring atom(s), may form an optionally substituted carbocycle (prefex-ably 5- to 6-membered ring) or an optionally substituted heterocyle (preferably 5- to 6-membered ring); or each combination of (R15 and R1G) and (R17and R18) taken together may fom oxo)
Compound (1-3) is preferably as follows.
(1) R1 is hydrogen.' R3 is hydrogen." m is 1 or 2; RH is hydrogen.
(2) mis 1 or 2, R is each independently halogen, halogenated lower alky], lower alkoxy, halogenated lower alkoxy, lower alkoxy lower alkyl, hydroxy lower alkyl, optionally substituted amino lower alkyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted carbamoyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue or sulfonylamino optionally substituted with lower alkyl; R1 is hydrogen.' R3 is hydrogen; R1'1 is hydrogen, hydroxyl or lower alkyl optionally substituted with mono- or di' lower alkylamino.' Z is O or NR19 (Rifl is hydrogen or lower alkyl, lower alkoxy lower alkyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue).
(3)11 is each independently, -F, -CFa, -OMe, "OCFa, "CHsOMe, -CH2OH, -CH2N(Me)2, -CONHMe, -CON(Me)2, -CH2PO(OEt)2, -PO(OEt)s, -NHSOsMe, or -NMeSChMe .'R1 is hydrogen; R3 is hydrogen; m is 1 or 2; RM is hydrogen, hydroxyl or -CHsN(Me)2; Z is 0 or NR'9(R'» is hydrogen or -CH(Me)2, -(CH2)20Me,
53

-(CH2)2PO(OEt)2).
(4)R15 and RIGare hydrogens; R17 and R18are hydrogens or taken together with the neighboring atom form a 3- to 7-membered carbocyleJ and/or Z is O or Nil. This case preferably also satisfys the above (2) or (3).

D ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on D ring are the same as those for A ring. The other symbols are as defined above.
The structure of compound (I) has at least the following characteristics.
(1) The main structure, condensed heterocycle, is substituted with oxo (=0), hydroxyl (OH) and oxo.
(2) A substituted carbamoyl group (-CONR]XR2) is attached to the position neighboring to the oxo grotip on the condensed hereocycle.
The above structure contributes to a remarkably potent integrase inhibitory activity and/or cell-growth inhibitory activity against virus including HIV. In contrast, the structures of the other parts such as ZI, Z2, and R3 each may be of variety, being optionally substituted or optionally condensed, and its condensed ring is also optionally substituted.
The present invention provides a pharmaceutically acceptable salt or a solvate of compound (I). All theoretically possible tautomer, geometrical isomer, optically active compound, and racemate thereof are within the scope of the invention.
Pharmaceutically acceptable salts of a compound of the present invention include, as basic salts, for example, alkali metal salts such as sodium or potassium salts.' alkaline-earth metal salts such as calcium or magnesium salts! ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine or procaine salts; aralkyl amine salts
54

such as N, N-dibenzylethylenediamine salts.' heterocyclic aromatic amine salts such as pyridin salts, picoline salts, quinoline salts or isoquinoline salts.' quaternary ammonium salts such as tetramethylammonium salts, totraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, mcthyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts. Acid salts include, for example, mineral acid salts such as hydrochloride, sulfates salts, nitrate salts, phosphates salts, carbonates salts, hydrogencarbonates or perchlorate; organic acid salts such as acetates, propionates, lactates, maleates,

fumarates, tararic acid salts, malates, citrates salts, ascorbates, formic acid;
sulfonates such as methanesulfonates, isethionates, benzenesulfonates, or p-toluenesulfonates.' and acidic amino acid salts such as aspartates or glutamates. Solvates of a compound of the present invention include alcholates and hydrates.
[0012]
A general process for producing the present compound will be exemplified below.
(Method of preparing raw material)
[Chemical formula 41]
55

(wherein L1 is a leaving group (e.g.; halogen); P' and P2 are a hydroxy protecting group.' P3 is a carboxy protecting group (e.g.: lower alkyl); Ra and Rb are hydrogen or a substituent on an amino group)
Examples of a hydroxy protecting group (P], P2) include acyl (e.g.: acetyl, pivaloyl, benzoyl), aralkyl (e.g.: benzyl), lower alkyl (e.g.: methyl), alkoxyalkyl (e.g.: methoxymethyl, methoxyethyl), lower alkylsulfonyl (e.g.: methanesulfonyl), arylsulfonyl (e.g.: benzenesulfonyl, toluenesulfonyl), alkoxycarbonyl (e.g.:
56

methoxycarbonyl) and the like.
As a carboxy protecting group (P;)), lower alkyl (e.g.; methyl, ethyl), and aralkyl (e.g.-' benzyl) are exemplified.
[0013]
(First step)
The present step is a reaction for condensing a compound (II) and a compound (III) to synthesize a compound (IV). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed. A compound (II) may be reacted as it is, or may be reacted after converted into corresponding acid chloride or active ester. Preferably, the reaction is performed in a suitable solvent in the presence of a condensing agent.
As a condensing agent, dicyclohexylcarbodiimide, l-ethyl'3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the like may be used. If necessary, a reagent such as l'hydroxybenzotriazole and N-hydroxysuccinirnide, or a base such as triethylamine, N-methylmorpholine, and pyridine may be added.
A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.
As a reaction solvent, a non-pvotonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4'dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.
A reaction time is a few minutes to a few tens hours, preferably 9 to 17 hours.
(Second step)
The. present step is a reaction for introducing a protected hydroxy group (OP1) into a compound (IV) to produce a compound (V), The reaction may be performed according to the condition for an alkoxylating reaction which is generally performed.
For example, a compound (V) in which P1 is methyl can be synthesized by reacting a compound (IV) with metal alkoxide (e.g.- sodium methoxide).
A reaction temperature is 0 to 200°C, preferably 80 to 1.20°C.
As a reaction solvent, alcohol, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 5 to 10 hours.
(Third step)
The present step is a reaction for protecting a hydroxy group of a compound
57

(V) to produce a compound (VI). The reaction may be performed according to the condition for a reaction of protecting a hydroxy group which is generally performed.
For example, by using diisopropyl azodicarboxylate or diethyl azodicarboxylate together with an alcohol and various phosphines, a compound (VI) in which P2 is alkyl can be synthesized.
A reaction temperature is 0 to 100°C, preferably 0°C to room temperature.
As a reaction solvent, THF, toluene, dichloromethane and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.
(Fourth step)
The present step is a reaction of oxidizing a nitrogen atom of a compoung (VI) to produce a compound (VII). The reaction may be performed according to the condition for an oxidation reaction using an oxidizing agent which is generally performed.
A reaction temperature is 0 to 100°C, preferably under ice-cooling to room temperature.
As a reaction solvent, chloroform, methylene chloride, acetic acid and the like are exemplified.
Examples of an oxidizing agent include metachloropcrbenzoic acid, hydrogen peroxide and the like.
A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.
(Fifth step)
The present step is a reaction for hydroxylating a methyl group of a compound (VII). Preferably, after acetoxylation by a reaction with acetic anhydride (reaction temperature- 0 to 150°C, preferably 120 to 140°C), this may be hydrolyzed (e.g.: treatment with a base (e.g.-' alkali metal hydroxide)).
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 2 hours for acetoxylation, and 0.6 to 1 hour for hydrolysis.

(Sixth step)
The present step is a reaction for oxidizing a hydroxy group of a compound (VIII) to synthesize a compound (IX).
A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.
58

As a reaction solvent, chloroform and the like are exemplified.
As an oxidizing agent, dimethyl sulfoxide and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.1 to 1 hour.
(Seventh step)
The present step is a reaction for oxidizing a formyl group of a compound (IX) to synthesize a compound (X).
A reaction temperature is 0 to 15CTC, preferably under ice-cooling to room temperature.
As a reaction solvent, an alcohol and the like are exemplified.
As an oxidizing agent, potassium hydroxide and iodine are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 3 hours.
(Eighth step)
The present step is a reaction for deprotecting an OP2 part of a compound (X) to synthesize a compound (XI). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.
A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.
As a reaction solvent, acetonitrile, methylene chloride, THF and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.
(Ninth step)
The present step is a reaction for deprotecting an OP1 part of a compound (XI) to synthesize a compound (I-A). The reaction may be treated preferably with a Lewis acid (e.g.: aluminum chloride).
A reaction temperature is 0 to 150°C, preferably 10 to 50°C.
As a reaction solvent, methylene chloride, THF and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.
(Tenth step)
The present step is a reaction for deprotecting an ester part (COOP3) of a
59

compound (X) to synthesize carboxylic acid (XII). Preferably, hydrolysis with an alkali (e.g.- NaOH) may be performed.
A reaction temperature is 0 to 150°C, preferably 10 to 50°C.
As a reaction solvent, methanol, water and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably a few minutes to 2 hours.
Carboxylic acid (XII) can be converted into various derivatives (e.g.; amide).
(Eleventh step)
The present step is a reaction for reacting' a compound (XII) with various amines to synthesize a compound (XIII). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed and, for example, the reaction may be performed as in the first step.
A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.
As a reaction solvent, a non-protonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.
A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.
An amide part of the resulting compound (XIII) may be further chemically modified (e.g.: N-alkylation).
(Twelfth step)
The present step is a reaction for deprotecting OP1 and OP2 parts of a compound (XIII) to synthesize a compound (TB). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.
For example, when pyridine hydrochloride is used, a reaction temperature is 0 to 200°C, preferably 150 to 180 degree.
A reaction time is a few minutes to a few tens hours, preferably 1 to 5 minutes.
(Thirteenth step)
The present, step is a reaction for deprotecting an ester part (COOP3) of a compound (XI) to synthesize carboxylic acid (XIV), Preferably, hydrolysis with an
60

alkali (e.g.'- lithium hydroxide) may be performed.
A reaction temperature is 0 to 150°C, preferably 10 to 50°C.
As a reaction solvent, methanol, water and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.
(Fourteenth step)
The present step is a reaction for deprotecting an OP1 part of a compound (XIV) to synthesize a compound (I"C). The reaction may be treated preferably with a Lewis acid (e.g." boron tribromide).
A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.
As a reaction solvent, dichloromethane and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably a few

A reaction time is a few minutes to a few tens hours, preferably a few mimites to 5 hours.

[0014]
The monocyclic carbamoylpyridone derivative obtained above is derived into a bicyclic compound by the following method.
(Process I)
[Chemical formula 42j
61

(wherein R', X, R-, P', P3 and R'f arc as define above, and L2 is a leaving group such as halogen etc.)
(Fifteenth step)
The present step is a reaction for reacting the compound (XI) or a compound (XD which is a tautomer thereof with an allyl compound to synthesize a compound (XV). A compound (XD can be synthesized, for example, according to the method of Example A-.I.
The reaction is performed preferably in the presence of a base (e.g.: cesium carbonate).
A reaction temperature is 0 to 100°C, preferably 10 to 40°C.
As a reaction solvent, dimethylformamide and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.
(Sixteenth step)
The present step is a reaction for oxidizing a compound (XV) to synthesize a compound (XVI). As an oxidizing agent, osmium tetraoxide and alkali metal osmium tetraoxide (e.g.KaOsO-i) are exemplified.
62

A reaction temperaturwe is 0 to 100°C, preferably 10 to 40°C.
As a reaction solvent, 1,4-dioxane, tetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.
(Seventeenth step)
The present step is a reaction for reacting a compound (XVI) with amine (XVII) to perform dehydration condensation to synthesize a compound (XVIII).
A reaction temperature is 0 to 200°C, preferably 140 to 180°C.
As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.
(Eighteenth step)
The present step is a reaction for deprotecting a compound (XVIII) preferably with an acid to synthesize a compound (XIX), and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.
A reaction temperature is 0 to 200°C.
As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.
As a reaction solvent, the acid and trimethylsily] iodide are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.
(Nineteenth step)
The present step is a reaction for reducing a compound (XVIII) to synthesize a compound (XX).
As a reducing agent, Ha/Pd C and the like are exemplified.
A reaction temperatuer is 0 to 100°C, preferably 10 to 30°C.
As a reaction sovelnt, dimethylformamide, methanol, tetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 5 to 20 hours.
[0015]
(Process 2)
63

The intermediate (XVIII) may be also synthesized by a method shown below.
[Chemical formula 43]

(Twentieth step)
The present step is a reaction for reacting a compound (XIV) with a compound (XXI) to synthesize a compound (XXII). The present reaction may be performed according to the condition for a conventional amidation reaction.
A reaction temperature is 0 to 100°C, preferably 0 to 50°C.
As a reaction solvent, dimethylformamide, methylene chloride, fcetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.
(Twenty-first step)
The present step is a reaction for reacting" a compound (XXII) with an acid to perform deprotection and intramolecular ring closure, to synthesize a compound (XXIII). The present reaction may be performed according to the condition for a conventional reaction of deprotecting acetal.
A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.
As a reaction solvent, dioxane, tetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1 hour.
As an acid, hydrochloric acid, and paratoluenesulfonic acid are exemplified.
(Twenty-second step)
The present step is a reaction for dehydrating a compound (XXHI) to
64

synthesize a compound (XXIV). The present reaction may be peformed according to the condition for a conventional dehydration reaction.
A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.
As a reaction solvent, acetonitrile, methylene chloride and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.
[0016]
(Process 3)
[Chemical formula 44]

(Twenty-third step)
The present step is a reaction for reacting a compound (XVI) with amine (XXIV) to perform dehydration condensation to synthesize a compound (XXV) according to the seventeenth step or a method of synthesizing a compound 17-1.
Preferably, as a reaction catalyst, an acid (e.g.- acetic acid) is added, and a microwave reaction apparatus is used.
A reaction temperature is 0 to 200°C, preferably 140 to 180°C.
As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.
(Twenty-fourth step)
65

The present step is a reaction for deprotecting a compound (XXV) preferably with an acid to synthesize a compound (XXVI) according to the eighteenth step, and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.
A reaction temprature is 0 to 200°C.
As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.
As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.
[0017]
(Process 4)
[Chemical formula 45]
66

(Twenty-fifth step)
The present step is a reaction for reacting a compound (XIV) with a compound (XXIV) to synthesize a compound (XXVII) according to the twentieth step.
The present reaction may be performed according to the condition for a conventional amidation reaction.
A reaction temperature is 0 to 100°C, preferably 0 to 50°C.
As a reaction solvent, dimethylformamide, methylene chloride, tetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.
(Twenty-sixth step)
The present step is a reaction for reacting a compound (XXVII) or a tautomer
67

thereof with an allyl compound to synthesize a compound (XXVIII) according- to the fifteenth step.
A reaction is performed preferably in the presence of a base (e.g.: cesium carbonate).
A reaction temperature is 0 to 100°C, preferably 10 to 40°C.
As a reaction solvent, dimethylformamide and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.
(Twenty-seventh step)
The present step is a reaction for oxidizing a compound (XXVIII) to synthesize a compound (XXIX) according to the sixteenth step.
As an oxidizing' agent, osmium tetraoxide and alkali metal osmium tetraoxide (e.g.: K2OSO4) are exemplified.
A reaction temperature is 0 to 100°C, preferably 10 to 40°C.
As a reaction solvent 1,4-dioxane, tetrahydrofuran and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferablky 1 to 5 hours.
(Twenty-eighth step)
The present step is a reaction for dehydration-condensing a compound (XXIX) to synthesize a compound (XXX) according to the seventeenth step or a method of synthesizing a compound 17-1. Preferably, as a reaction catalyst, an acid (e.g.: acetic acid) is added, and a microwave reaction apparatus is used.
A reaction temperature is 0 to 200°C, preferably 140 to 180°C.
As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.
(Twenty ninth step)
The present step is a reaction for deprotecting a compound (XXX) preferably with an acid to synthesize a compound (XXXI) according to the eighteenth step, and may be peformed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.
A reaction temperature is 0 to 200°C

A reaction temperature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.
As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.
A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 houi[0018]
(Process 5)
A compound (1-3) in which Z is NR19 can be synthesized according to the following reaction scheme, according to Process 4.
[Chemical formula 46)
69

70

(wherein respective symbols are as defined above)
(Forty-ninth step)
A compound (XIV-16) is obtained by reacting a compound (XIV) with an amine reagent, according to the thirty-fifth step.
(Fiftieth step)
A compound (XIV-17) is obtained by subjecting a compound (XIV-16) to a general acetal deprotecting reaction according to the forty-fourth step.
(Fifty-first step)
A compound (XIV-18) is obtained (D ring formation) by deprotecting a P1 part of a compound (XIV-.14) according to the thirty-eighth step.
[0020]
The present invention further provides various intermediates (I-P) shown below and a process for preparing the same, as well as a process for preparing the above mentioned compound (I) comprising the deprotection of the intermediate.
(Intermediates)
71

(P1 is a hydroxyPprotecting group! the other symbols are as defined above)
Preferred compounds are shown below. Each P1 is a hydroxyPprotecting group, such as CG narylCi-salkyl (e.g., benzyl (=Bn)).

Preferably, wherein Rc is one or two halogen; R»- is Cinalkyl, Ce-i.iarylCiBalkyl, Cc-naryl, or alkoxy; and P1 is CciHarylCi-salkyl;

Preferably, wherein .Rc' is one or two halogen! and P1 is Ce-warylCi-Balkyl;
72
Preferably, wherein Re is one or two halogen! Rz is Ci-salkyl, CflMarylCi-aalkyl, Cfi-i-iaryl, or alkoxy." and P1 is CfiMarylCisalkyl!

Preferably, wherein R° is one or two halogen; and P1 is Cc-MarylCi-aalkyl,"

Preferably, wherein Rc is one or two halogen; and P1 is Cfii-iarylCisalkyl;

Preferably, wherein Re is one or two halogen! and P1 is Coi-iarylCiHalkyl;

Preferably, wherein R° is one or two halogen,' and P1 is CsLiarylCi-salkyl;

Preferably, wherein Rc is one or two halogen,' and P1 is Cei'iarylCiaalkyl;
73

Preferably, wherein Ha is one or two halogen; R* is Ci-salkyll RyA is Ivydrogen, C3 ccycloalkyl, , heterocycle, or Ci-aalkyl optionally substituted with hydroxy, C.-j-fiCycloalkyl, alkoxy, heterocycle, heteroaryl, CG naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-salkyl;

Preferably, wherein RQ is one or two halogen,' Rz is Ci-salkyl; R'-1 is hydrogen, C3Gcycloalkyl, , heterocycle, or Ciaalkyl optionally substituted with hydroxy, C3-Gcycloalkyl, alkoxy, heterocj'de, heteroaryl, CG naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-alkyl or Cisalkyl; and P1 is Cc-i'iarylCi-salkyl;

Preferably, wherein Rc is one or two halogen; Rzl is hydrogen, Cs-ficycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, Cocycloalky], alkoxy, heterocycle, lieteroaryl, Cfii-iaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or CisalkyL'and P1 is Co-MarylCi-salkyH
74

Preferably, wherein Rc is one or two halogen! Rzl is hydrogen, Ca-ccycloalkyl, , heterocj'cle, or Ci-salkyl optionally substituted with hydroxy, Cs-ccycloalkyl, alkoxy, heterocycle, heteroaryl, Cn-i-iaryl, or amino, whei-ein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-salkyl; and P1 is CGMarylCi-aalkyl;

Preferably, wherein R" is halogen! and P1 is CG I-iarylCi-salkyl!
The above intermediates, compound (I-20a), (I-20b), (I-21a), (1-2Ib), (I-22a), (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (1-25), (1-26), or (1-27), can be prepared by condensing a compound of the formula!

wherein 11° is one or two halogen! and R.00 is Ci-salkyl!
with each amine shown below, respectively:

wherein 11'-is Ci aalkyl, Co-i-iarylCi-salkyl, Ce-i.iaryl, or alkoxy!
75

wherein R'- is Ci-aalkyl, CG uarylCrsalkyl, Ce-naryl, or alkoxyi

wherein R'- is Cisalkyl; Rzl is hydrogen, Caecycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, C3 ocycloalkyl, alkoxy, heterocycle, heteioaryl, Cfi-naryl, or amino, wherein said amino may be optionally substituted with -C(0)C18alkyl or Ci-salkyl;

wherein Rz is Ci-salkyl; Rzl is hydrogen, Ca-Gcycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, Ca-Gcycloalkyl, alkoxy, heterocycle, hcteroaryl, CG naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Cisalkyl;

wherein R'-' is hydrogen, C:i-6cycloalkyl, , heterocycle, or Ci-aalkyl optionally substituted with hydroxy, C;j ocycloalkyl, alkoxy, heterocycle, heteroaryl, Ce-naryl, or amino, wherein said amino may be optionally substituted with - C(0)Ci-8alkyl or CialkyL'
76

wherein Rzl is hydrogen, Caccycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, Cs-ocycloalkyl, alkoxy, heterocycle, heteroaryl, Cc-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-salkyl;

The condition for the above condensation is illustrated below for example.
Examples of the solvent include halocarbons such as dichloromethane, dichloroethanc, and acetic acid.
The reaction temperature is preferably, 0 to 200 °C, more preferably, 50 to 170°C.
The reaction time is usually several minutes to several hours.
The above intermediates, compound (I"20a), (I-20b), (I-21a), (I-21b), (I.-22a), (I-22b), (I-23a), (I"23b), (I-24a), (I-24b), (1-25), (1-26), or (1-27), can be deprotected to give each corresponding deprotected compound wherein P1 is hydrogen, or its pharmaceutical acceptable salt, which are encompassed within the scope of compound (I) of the present invention.
In addition, the present compound obtained above may be further chemically modified to synthesize another compound. In addition, when there is a reactive functional group (e.g.: OH, COOH, NH2) on a side chain part etc. in the above reaction, the group may be protected before the reaction and may be deprotected after the reaction, if desired.
The present compound is useful, for example, as a drug such as an anti-virus drug. The present compound has the remarkable inhibitory action on integrase of a virus. Therefore, the present compound can be expected to have the preventive or
77

therapeutic effect for various diseases derived from a virus which produces at least integrase, and is grown at infection in an animal cell, and is useful as an integrase inhibiting agent for retrovirus (e.g. HIV-1, HIV-2, HTLV-1, SIV, FIV etc.), and is useful as an anti-HIV drug etc.
In addition, the present compound may be used in joint use therapy by combining an anti-HIV drug having the different action methanism such as a reverse trascriptase inhibiter and/or a protease inhibiting agent. Particularly, currently, an integrase inhibiter is not marketed, and it is useful to use in joint use therapy by combining the present compound with a reverse transcriptase inhibiter and/or a protease inhibiter.
Further, the above use includes not only use as a medical mixture for anti-HIV, but also use as a joint use agent for increasing the anti-HIV activity of other anti-HIV drug such as cocktail therapy.
In addition, the present compound can be used in order to prevent infection with a retrovirus vector from spreading into a tissue other than an objective tissue, upon use of a retrovirus vector based on HIV or MLV in the field of gene therapy. Particularly, when a cell is infected with a vector in vitro, and the cell is returned into a body, if the present compound is administered in advance, extra infection can be prevented in a body.
The present compound can be adminitetered orally or parenterally. In the case of oral administration, the present compound can be also used as a conventional preparation, for example, as any dosage form of a solid agent such as tablets, powders,

granules, capsules and the like.' an aqueous agent; an oily suspension; or a liquid agent such as syrup and elixir. In the case of parenteral administration, the present compound can be used as an aqueous or oily suspension injectable, or a nasal drop. Upon preparation of it, conventional excipients, binders, lubricants, aqueous solvents, oily solvents, emulsifiers, suspending agents, preservatives, stabilizers and the like may be arbitrarily used. As an anti-HIV-drug, particularly, an oral agent is preferable. A preparation of the present invention is prepared by combining (e.g. mixing) a therapeutically effective amount of the present compound with a pharmaceutical acceptable carrier or diluent.
A dose of the present invention is different depeniding on an administration method, an age, a weight and conditionn of a patient, and a kind of a disease and, usually, in the case of oral administraton, about 0.05mg to 3000mg, preferably about O.lmg to lOOOmg may be administered per adult a day, if necessary, by dividing the
78

dose. In addition, in the case of parenteral administration, about O.Olmg to lOOOmg, preferably about 0.05mg to 500mg is administered per adult a day-
Examples are shown below.
[0025]
Example A'l)
9-Hydroxy-2-(2-methoxy-ethyl)-l)8-dioxo-l,8-dihydro-2H-pyrid[l,2-a]pyrazine
-7-carboxylic acid 4-fluorobanzylamide
Example B-l)
9-Hydroxy-2-(2-methoxy-e thy l)-l,8-dioxo-1,3,4,8-fcetrahydro-2H-pyrid[l,2-a]py
razine-7-carboxylic acid 4"fluoro-benzylamide
79
[Chemical formula 52j

l) Mantol] (189g, l.Smol) was dissolved in dimethylformamide (1890ml), and benzyl bromide (184ml, 1.5mol) was added. After the solution was stirred at 80°C for 15 minutes, potassium carbonate (228g, 1.65mol) was added, and the mixture was stirred for 1 hour. After the reaction solution was cooled to room temperature, an inorganic salt was filtered, and the filtrate was distilled off under reduced pressure. To the again precipitated inorganic salt was added tetrahydrofuran (lOOOrnl), this was filtered, and the filtrate was distilled off under reduced pressure to obtain the crude product (329g, >100%) of 3-benzyloxy-2-methyl-pyraiv4-one 2 as a brown oil.
NMR (CDCla)6: 2.09(31-1, s), 5.15(2H, s). 6.36(1H, d, J=5.6Hz), 7.29-7.4l(5H, m), 7.60(1H, d, J=5.6Hz).
2) The compound 2 (162,2g, 750mmol) was dissolved in ethanol (487ml), and aqueous ammonia (28%, 974ml) and a 6N aqueous sodium hydroxide solution (150ml, 900mmol) were added. After the reaction solution was stirred at 90 °C for 1 hour, this was cooled to under ice-cooling, and ammonium chloride (58g, 1080mmol) was added. To the reaction solution was added chloroform, this was extracted, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, isopropyl alcohol and diethyl ether were added to the residue, and precipitated crystals were filtered to obtain 3"benzyioxy"2-methyMH-pyridine-4-one 3 (69.lg, 43%) as a pale yellow crystal.
NMR (DMSO-dc)8: 2.05(3H, s), 5.04(2H, s), 6.14(lH, d, J=7.0Hz), 7.31-7.42(5H, m), 7.46(1H, d, J=7.2Hz), 11.29(lH, brs).
80

3) The above compound 3 (l29g, 599mmol) was suspended in acetonitrile (1300ml), and N-bromosuccinic acid imide (l17g, 659mmol) was added, followed by stirring at room temperature for 90 minutes. Precipitated crystals were filtered, and washed with acetonitrile and diethyl ether to obtain
3-benzyloxy5-bromo-2-methyl-pyridine-4-ol 4(l54g, 88%) as a colorless crystal.
NMR (DMSO-d(j)8: 2.06(3H, s), 5.04(2H. s), 7.32-7.42(5H, in), 8.03(lH, d, J=5.5Hz), 11.82(1H, brs).
4) To a solution of the compound 4 (88g, 300mmol), palladium acetate (13.4g, 60mmol) and l,3-bis(diphenylphosphino)propane (30.8g, 516mmol) in dimethylformamide (660ml) were added methanol (264ml) and triethylamine (210ml, 1.5mol) at room temperature. The interior of a reaction vessel was replaced with carbon monoxide, and the material was stirred at room temperature for 30 minutes, and stirred at 80 degree for 18 hours. A vessel to which ethyl acetate (1500ml), an aqueous saturated ammonium chloride solution (1500ml) and water (1500ml) had been added was stirred under ice-cooling, and the reaction solution was added thereto. Precipitates were filtered, and washed with water (300ml), ethyl acetate (300ml) and diethyl ether (300ml) to obtain 5-benzyloxy-4-hydroxy-6methylnicotinic acid methyl ester 5 (44.9g, 55%) as a colorless crystal.
NMR (DMSO-dc)S: 2.06(3H, s), 3.72(3H, s), 5.02(2H, s), 7.33-7.42(5H, m), 8.07(1H, s).
5) After a solution of the compound 5 (l.9.1g, 70mmol) in acetic anhydride (134ml) was stirred at 130 °C for 40 minutes, the solvent was distilled off under reduced pressure to obtain 4-acetoxy-5-benzyloxy6-methyl'nicotinic acid methyl ester 6 (19.9g, 90%) as a flesh colored crystal.
NMR(CDCla)6: 2.29(3H, s), 2.52(3H, s), 3.89(3H, s), 4.98(2H, s), 7.36-7.4l(5H, m), 8.85(1H, s).
6) To a solution of the compound 6 (46.2g, 147mmol) in chloroform (370ml) was added metachloroperbenzoic acid (65%) (42.8g, 161mmol) in portions under ice-cooling, and this was stirred at room temperature for 90 minutes. To the reaction solution was added a 10% aqueous potassium carbonate solution, and this was stirred for 10 minutes, followed by extraction with chloroform. The organic layer was washed with successively with a 10% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and

ammonium chloride solution, and an aqueous saturated sodium chloride solution, and
81

dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diisopropyl ether to obtain 4-acetoxy-5-benzyloxy-6-methyl-].-oxy-nicotinic acid methyl ester 7 (42.6g, 87%) as a colorless crystal.
NMR (CDC13)6: 2.30(3H, s), 2.4l(3H, s), 3.90(3H, s), 5.02(211, s), 7.37-7.39(5H, ra), 8.70(1H, s).
7) To acetic anhydride (500ml) which had been heated to stir at 130 °C was added the compound 7 (42.6g, 129mmol) over 2 mintues, and this was stirred for 20 minutes. The sovent was distilled off under reduced pressure to obtain 4'acetoxy-6-acetoxymethyl'5-benzyloxy-nicotinic acid methyl ester 8 (49.6g, >100%) as a black oil.
NMR (CDC13)S: 2.10(3H, s), 2.28(3H, s), 3.9l(3H, s), 5.07(2H, s), 5.20(2H, s), 7.35-7.4l(5H, m), 8.94(lH, s).
8) To a solution of the compound 8 (46.8g, 125mmol) in methanol (140ml) was added a 2N aqueous sodium hydroxide solution (376ml) under ice-cooling, and this was stirred at 50 °C for 40 minutes. To the reaction solution were added diethyl ether and 2N hydrochloric acid under ice-cooling, and precipitated crystals were filtered. Resulting crystals were washed with water and diethyl ether to obtain 5-ben'zyloxy-4-hydroxy6-hydroxymethyl-nicotinic acid 9 (23.3g, 68%) as a colorless crystal.
NMR (DMSO-d(i)5: 4,49(2H, s), 5.19(2H, s), 5.85(lH, brs), 7.14-7.20(2H, m), 7.33-7.43(7H, m), 8.30(lH, s), 10.73(lH, t, J=5.8Hz), 11.96(lH, brs).
9) To a solution of the compound 9 (l3lg, 475mmol), l-(3-dirnethylaminopropyl)-3-ethylcarbodiimide hydrochloride (219g, 1.140mmol) and 1-hydroxybenzotriazole (l28g, 950mmol) in dimethylformamide (1300ml) was added 4-fluorobenzylamine (109ml, 950mmol), and this was stirred at 80°C for 1.5 hours. After the reaction solution was cooled to room temperature, hydrochloric acid was added, followed by extraction with ethyl acetate. The extract was washed with a 5% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a mixture (l75g) of 10 and 11, the resulting mixture, was dissolved in acetic
82

acid (1050ml) and water (1050ml), and zinc (31.lg, 475mmol) was added, followed by heating to reflux for 1 houx*. After the reaction solution was cooled to room tempreture, a 10% aqueous potassium carbonate solution was added, followed b}' extraction with ethyl acetate. The extract was washed with an aqueous satxix-ated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dx'ied with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, this was washed with diethyl ether to obtain 5_beiizyloxy-N-(4-fluox-o'benzyl)-4-hydroxy-6-hydroxymethyl-nicotinic acid amide 10 (l07g, 59%) as a colorless cx-ystal.
NMR (DMSO-dc)6: 4.45(2H, d, J=4.3Hz), 4.52(2H, d, J=5.8Hz), 5.09(2.H, s), 6.0l(lH, brs), 7.36-7.43(5H, m), 8.3l(lH, s), 12.63(lH, brs).
10) After maixganese dioxide (49g) was added to a suspension of the compound 10 (9.8g, 25.6mmol) in chloroform (490ml), the mixture was stirred at room temperature for 1 hour. After the reaction solution was stirred at 60 °C for 20 minutes, Celite filtration was performed, and this was washed with chloroform heated at 50 °C. The filtrate was distilled off under reduced pressure to obtain 5-benzyloxy-N-(4'fluorobenzyl)-6-foi*myl-4-hydx-oxynicotinic acid amide 12 (8.2g, 84%) as a pale yellow crystal.
NMR (DMSO-d)8: 4.53(2H, d, J=5.8Hz), 5.38 (2H, s), 7.15-7.2l(2H, m), 7.35-7.46(711, m), 8.33(1H, s), 9.90(lH, s), 10,35(lH, t, J=5.8Hz), 12.49(1H, brs).
11) To an aqueous solution (105ml) of sodium chlorite (7.13g, 78.8mmol), and sulfamic acid (7.65g, 78.8mmol) was added a solution of the compound 12 (15.Og, 39.4mmol) in tetrahydrofuran (630ml) under ice-coling, and the mixture was stirred at room temperature for 1 hour. After water (2500ml) was added to the x-eaction solution, precipitated crystals were filtered. Washing with diethyl ether afforded 3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-hydx-oxy-pyridine-2-carboxylic acid 13 (14.0g, 90%) as a coloi-less cx-ystal,
NMR (DMSO-dfi)8: 4.52(2H, d, J=5.8Hz), 5.13 (2H, s), 7.14-7.19(2H, m), 7.31-7.40(5H, m), 7.47-7.49(2H, m), 8.3l(lH, d, J=4,5Hz), 10.44(1H, t, J=5.9Hz), 12.47(lH, brs).
12) A solution of the compound 13 (l98mg, 0.500mmol), 1.-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (ll5mg, 0.600mmol) and 1-hydroxybenzotriazole (81mg, 0.600mmol) in dimethylformamide (3ml) was
83

stirred at room temperature for 1.5 hours. Then, methanol (3ml) and triethylamine (153ul, l.lOmmol) were added, and the mixture was heated to reflux for 1.5 hours. The reaction solution was diluted with ethyl acetate, washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain 3-benzyloxy-5-(4_fluoro"benzylcarbamoyl)-4-hydroxy "pyridine-2-carboxylic acid methyl ester 14 (141 nig, 69%) as a colorless crystal.
NMR (DMSO-dG)5: 3.85(3H, s), 4.52(2H, d, J=6.0Hz), 5.15(2H, s), 7.13-7.2l(2H, m), 7.31-7.47(71-1, m), 8.33(Ui, s), 10.4l(lH, t, J=6.0Hz), 12.59QH, brs).
13) After 3-bromopropene (2.15ml, 24.8mmol) was added to a solution of the compound 14 (6.79g, 16.5mmol), and cesium carbonate (8.09g, 24.8mmol) in dime thy lformamide (54ml), the mixture was stirred at room temperature for 4.5 hours. To the reaction solution was added an aqueous ammonium chloride solution, and this

was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
l'allyl-3 •benzyloxy5-(4-fluoro-benzylcarbamoyl)-4-0x0-l,4-dihydro-pyridine-2-carboxy lie acid methyl ester 15 (6.15g, 83%) as a colorless crystal.
NMR (CDCla) 6: 3.76(3H, s), 4.54(2H, d, J=6.0Hz), 4.60(2H, d, J=6.0Hz), 5.20-S.37(2H. m), 5.25(2H, s), 5.80-5.93(lH, m), 6.98-7.04(2H, m), 7.31-7.35(7H, m), 8.45(lH, s), 10.4K1H, m).
14) To a solution of the compound 15 (7.6g, 16.9mmol) in 1,4-dioxane (228ml) was added an aqueous solution (38ml) of potassium osmate dihydrate (372mg, l.Olmmol), and sodium metaperiodate (14.5g, 67.6mmol) was further added, followed by stirring at room temperature for 2 hours. The reaction solution was added to a vessel to which ethyl acetate (300ml) and water (300ml) had been added, while stirring. The organic layer was washed with water, a 5% aqueous sodium hydrogen sulfite solution and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
84

3-benzy]oxy5-(4-fluoro-benzylcarbamoyl)-4-oxo-l-(2-oxo-ethyl)-l,4-dihydro-pyridine-2 •carboxylic acid methyl ester 16 (5.39g, 71%) as a colorless crystal.
NMR (CDCIs)6: 3.74(3H, s), 4.60(2H, d, J=5.9Hz), 4.87(2H, s), 5.27(2H, s), 6.98-7.04(2H. m), 7.30-7.40(7H, m), 8.39(lH, s), 9.58(1H, s), 10.38(1H, s).
15) To a solution of the compound 16 (400mg, 0.884mmol) in methylene chloride (12ml) were added 2-methoxyethylamine (77ul, 0.884mmol) and acetic acid (18ul), and the mixture was stirred at room temperature for 5 minutes. Thereafter, the reaction was performed at 140 °C for 30 minutes in a microwave reaction apparatus. The solvent was distilled off under reduced pressure, the residue was subjected to silica gel column chromatography, and fractions eluting with toluene-acetone were concentrated under reduced pressure to obtain
9-benzyloxy2-(2-methy-ethyl)'l,8-dioxo-l,8-dihydro-2H-pyrid[l,2-a]pyrazine'7"carbox ylic acid 4-fluoro-benzylamide 17-1 (226mg, 54%) as a yellow solid.
NMR (CDC13)5: 3.35(3H, s), 3.65(2H, t, J=5.1Hz), 3.97(2H, t, J=4.5Hz), 4.63(2H, d, J=5.7Hz), 5.28(2H, s), 6.56(2H, m), 7.01(2H, t, J=8.7Hz), 7.38-7.30(5H, m), 7.65(2H, d, J=6.6Hz), 10.63(1H, s).
16) To the compound 17-1 (l40mg, 0.293mmol) was added trifluoroacetic acid (l.4ml) under ice-cooling, and the mixture was stirred at 0 °C for 5 minutes and, then, at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water. This was washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution and water, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized with methylene chloride-ethanol to obtain Example A-1 (89mg, 79%) as a yellow crystal,
melting point: 223-224 °C
NMR (DMSO-dc,)8: 3.25(3H, s), 3.58(2H, t, J=5.4Hz), 3.92(2H, t, J=5.1Hz), 4.53(2H, d, J=5.7Hz), 6.87(1H, d, 6.3Hz), 7.14(2H, t, J=9.0Hz), 7.33-7.38(2H, m), 7.47(lH, d, J=6.0Hz), 8.77(1H, s), ,10.56(lH, t, J=6.0Hz), 12.00(1H, brs).
17) The compound 17" 1 (l57mg, 0.329mmol) was dissolved in dimethylformami.de (18ml) and methanol (iml), 10% palladium-carbon powder (31mg) was added, and the mixture was stirred at room temperature for 20 hours under the hydrogen atmosphere. The reaction solution was filtered with Celite, and the filtrate was
85

concentrated under reduced pressure. The residue was dissolved in chloroform, this was filtered with Celite again, and the filtrate was concentrated under reduced pressure. The residue was recrystallized with methylene chloride-methanol to obtain Example B-l (6Gmg, 52%) as a browm crystal,
melting point: 197-199 °G
NMR (DMSO-dG)6:3.27(3H, s), 3.55(2H, t, J=5.1Hz), 3.68(2H, t, J=5.1Hz), 3.79(2H, s), 4.36(2H, s), 4.5K2H, d, J=5.7Hz), 7.15(2H, t, J=8.7Hz), 7.32-7.37(2H, m), 8.38(1H, s), 10.46(1H, t, J=5.4Hz), 12.4l(lH, s).
Example Ol
[Chemical formula 55]

l) A compound 33 was synthesized using laminomethylcyclopentanol hydroxyethylamine according to the method of synthesizing a compound 17-1.
1H-NMR (CDCI;J)6: 1.3(M.80(lOH, m), 3.47(lH, d, J=11.4Hz), 3.6l(lH, d, J=11.4Hz), 3.80-3.95(111, m), 4.30(lH, dd, J=14.7, 3.0Hz), 4.60(2H, d, J=5.7Hz), 5.17-5.23(2H, m), 5.39(111, d, J=9.9Hz), 6.95-7.10(2H, m), 7.20"7.40(5H, m), 7.58(2H, d, J=7.2Hz), 8.41(1H, s), 10.400.H, s).
2) A compound 33-2 was synthesized using hydroxyethylamine according to the similar method.
Compound 33-2)
5-Benzyloxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-l-oxa-3a,8a-diaza-cyclopenta[b]naphtha lene-7-carboxylic acid 4-fluorobenzylamide
1H-NMR (DMSO-d6)8: 3.48-3.58(1H, m), 3.73-3.86UH, m), 3.97-4.10(2H, m), 4,20-4.30(1H, m), 4.46-4.60(2H, m), 4.85(lH, dd, J=12.3, 3.5Hz), 5.40(1H, d, J=10.2Hz),
86

5.18(1H, d, J=10.2Hz), 5.28(1H, dd, J=10.2, 3.2Hz), 7.10-7.20(2H, m), 7.23-7.40(5H, m), 7.50-7.73(2H, m), 8.60C1H, s), 10.22(1H, m).
3) Example C-l was synthesized using a compound 33, according to the method of synthesizing Example A-1.
Melting point: >300°C

1H-NMR (DMSO-dfi)5.- 1.10-1.60(10H, m), 3.25(1H, d, J=11.4Hz), 3.37(1H, d, J=11.4Hz), 3.76(1H, t, J=10.5Hz), 4.30(2H, d, J=5.8Hz), 4.66(IH, dd, J=12.2, 3.8Hz), 5.22(111, dd, J=3.8, 10.4Hz), 6.90-6.96(2H, m), 7.10-7.15(2H, m), 8.25QH, s), 10.10(1H, brs), 11.32(1H, brs).
The following compounds were synthesized using the similar method.
Example C-2)
5-Hydroxy-4,6-dioxo-2,3l4,6,9,9a'hexahydro-l-oxa-3a,8a-diaza-cyclopentafb]naphthalene-7-carboxylic acid 4-fluorobenzylamide
Melting point: 272-274 °C
1PI-NMR (DMSOdG)6: 3.59-3.67(IH, m), 3.72-3.8 KIH, m), 3.98-4.10(2H, m), 4.27-4,35(IH, m), 4.52(2H, d, J=7.2Hz), 4,92(.1H, dd, J=12.3, 12.3Hz), 5.27(IH, dd, J=3.6, 9.9Hz), 7.11-7.20(2H, m), 7,30-7.40(2H, m), 8.49(IH, s), 10.32(1H, t, J=5.6Hz), 11.53(1H, s).
Example C-3)
5-Hydroxy "6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a-diazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 259 °C
1H-NMR (DMSO-d6)6: 1.60-1.67(1H, in), 1.72-1.85(IH, m), 3.25(1H, td, J=12.8, 3.5Hz), 3.86-3.930.H, m), 4.06(IH, dd, J=11.4, 4,2Hz), 4.44-4.57(5H, m), 5.28(IH, t, J=3.8Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8.5K.1H, s), 10.36(IH, t, J=6.0Hz), 12.47(IH, s).
Example C-4)
5-Hydroxy-l-isopropyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-lH-l,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 232-234°C
NMR (DMSO-dfi)8: 1.03(3H, d, 6,6Hz), 1.14(3H, d, 6.6Hz), 2.79-3.66(5H, m), 3.82(IH, t, 10.8Hz), 4.51(3H, in), 4.90(1H, ra), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.45(Ili, s),
87

10.39(1H, t, 5.4Hz), 11.60(1H, s).
Example 05)
5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-lH-l,3a,8a-triaza-cyclopenta[b] nap hthalene'7-carboxylic acid 4-fluoro-benzylamide
melting point: 256-258 °C
NMR (DMS0-dG)6: 3.00"3.55(5H, m), 3.96(1H, t, 11.4Hz), 4.52(2H, d, 11.7Hz), 4.76(2H, m), 7.16(2H, t, 8.7Hz), 7.35(2H, m), 8.48(IH. s), 10.42(IH, t, 5.4Hz), 11.9l(IH, B).
Example C-6)
5-Hy droxy-6,10-dioxo-1,2,3,4,6,9,9a, 10-octa hydro-1,4a, 8a" triaza "anthracene-7-carboxylie acid 4-fluoro-benzylamide
melting point-' 255°C
NMR (DMSO-d6)6: l.60(lH, s), 2.75-3.16(4H, m), 4,52(2H, d, 6.0Hz), 4,13"4.68(4H, m), 7.16(2H, 9.0Hz, t), 7.34(2H, m), 10.42QH, s), 10.44(IH, 6.0Hz, t), 12.81(IH, s).
Example 07)
l-(2-Diethylamino-ethyl)-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a"hexahj'dro-lH"l,3a,8a-triaza-cj'clopentalb]naphthalene"7-carboxylic acid 4-fluoro-benzylamide
melting point: 186-187 °C
NMR (DMSOdo)S: 0.97(6H, t, 7.2Hz), 2.42-2.9l(lOH, m), 3.44-3.87(5H, m), 4.23(IH, m), 4,5l(2H, d, 5.7Hz), 5.00(IH, m), 7.16(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.43(IH, s), 10.39(1H, t, 5.7Hz), 11.8l(IH, s).
Example 08)
l-Hydroxy-2,ll-dioxo'2,5,5a,7,8,9,10,ll-octahydro-6oxa"4a, 10a-diaza-cyclohepta[b]naphthalene-Scarboxylic acid 4-fluoro-benzylamide
melting point: 242-244 °C
NMR (DMSO-dG)8: 1.40-2.00(4H, m), 3.20-3.30(IH, m), 3.66-3.77(2H, m), 4.14-4.23(IH, m), 4,38-4.41(11-1, m), 4.52(2H, d, 6.3Hz), 4.58-4.63(IH, in), 5.34(IH, brs), 7.15(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.50(IH, s), 10.39(311, brs), 12.14(IH, s).
Example 09)
5-Hydroxy-l-(2-hydroxy-ethyl)-6,40-dioxo-l,2J3,4,6,9,9a,10-octahydro-].,4a,8a-triaza-anthracene"7-carboxylic acid 4fluoro-benzylamide
88

NMR (DMSOdfi)8: 1.58-1.80(IH, m), 2.70-3.60(7H, m), 4.40-4.54(6H, m), 4.77-4,82(IH, m), 7.15(2H, t, 9.0Hz), 7.33-7.38(2H, m), 8.52(1H, s), 10.43(IH, brs), 12.57(IH, s).
Example O10)
l-Hydroxy-21.l.l-dioxo-2,5a,6,7,8,9,10,ll-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluoro-benzylamide
melting point: 256°C
NMR (DMSO-dc)S: 1.47-1.77(4H, m), 2.69-2.8l(2H, m), 3.34-3.4l(lH, m), 4.08-4.l2(IH, m), 4,26-4.40(2H, in), 4.52(2H, d, J=6.0Hz), 7.15(2H, t, 8.8Hz), 7.33-7.36(2H. m), 8.43(1H, s), 10.46(1H, t, J=6.0Hz). 12.68(IH, s).
Example C-ll)
f5-Hydroxy-l-(2-methoxy-ethyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 147°C
NMR(DMSO-d6)6: 1.56-1.74(2H, m), 2.53-2.58(lH, m), 2.66-3.10(4H, m), 3.18(3H, s), 3.41-3.39(2H, m), 4.37-4.52(5H, m), 4.73-4.80(IH, m), 7.15(2H, t, 8.8Hz), 7.33-7.37<2H, m), 8.56(1H, s), 10.40UH, t, J=6.0Hz), 12.62(IH, s).
Example C-12)
5-Hydroxy-l-(2-isopropoxy-ethyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylie acid 4-fluoro-benzylamide
melting point: 151 °C
NMR (DMSO-dc)8: 1.02(6H, dd, J=4.0, 6.0Hz), 1.56-.l.67(2H, m), 2.53-2.58(lH, m), 2.74-3.04(4H, m), 3.18(3H, s), 3.41-3.52(3H, m), 4.41-4.59(5H, m), 4.79-4,83(.lH, m), 7.15(2H, t, 8.8Hz), 7.34-7.36(2H, m), 8.58(IH, s), 10.40(1H, t, J=6.0Hz), 12.56(IH, s).
Example C-13)
5-Hydroxy-3,3-dimethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydrn-2H-loxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting-point: 275-277 °C
NMR (DMSO-dc)8: 2.97(3H, s), 3.0K3H, s), 3.00-3.18(3H, m), 4.45-4.56(5H. m), 5.16(1H, s), 7.15(2H. t, J=9Hz), 7.35(2H, dd, J=5.4Hz, 8.7Hz), 8.5l(lH, s), 10.36(1H, t, J=5.7Hz), 12.4(1H, s).
89

Example C-14)
l-Cyclohexyl-5-hydroxy-6,10-dioxe-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthrace ne-7-carboxylic acid-4-fluoro-benzylamide
melting point: 275-277 °C
NMR (DMS0-dfi)5: 1.22-1.70(2H, m), 2.50-3.02(3H, in), 4.45(411, m), 4.52(2H, s), 4.78(1H, d, J=13.2Hz), 7.16(2H, t, J=8.7Hz), 7.35(2H, dd, J=5.7Hz, 8.4Hz), 8.62(lH, s), 10.52(1H, s). 12.55(1H, s).
Example Ol5)
5-Hydroxy-l-isopropyl-6,10-dioxo-1,2,3,4,6,9,9a, 10-oxtahydro-l,4a,8a-triaza-anthrace ne-7"carboxylic acid-4-fluorcrbenzylamide
melting point: 220 °C
NMR (DMSO-de)fi: 0.94(6H, d, J=9.6Hz), 1.53-1.67(2H, m), 2.92-3.30(3H, m), 4.32-4.40(4H, m), 4.52(2H, d, J=5.7Hz), 4.89(lH, d, J=14.1Hz), 7.16(2H, t, J=9.0Hz), 7.35(2H, dd, J=6.3Hz, 9.0Hz), 8.6l(lH, s), 10.46(1H, s), 12.55(lH. s).
Example C-16)
5-Hydroxy-3,3-dimethyl-6, lOdioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-tiiaza-anthrac ene-7-carboxylic acid 4'fluoro'benzylainid.e
melting point-' 280 °C
NMR (DMSO-de)S: 0.87(3H, s), 0.93(3H, s), 2.59-3.15(6H, m), 4.09-4,57(611, m), 7.14(2H, d, J=9.0Hz), 7.34(2H, dd, J=5.4Hz, 8.4Hz), 8.42(lH, s), 10.46(l.H, s), 12.77(1H, s).
Example Ol7)
5-Hydroxy-l-(2-morpholin-4-yl-2-oxo-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4 a,8a-triaza-anthracene-7-carboxylie acid 4-fluoro-benzylamide
melting point: 140 °C
NMR (DMSO-dfi)8: 1.60(2H, m), 2.91-3.62(13H, m), 4.4K2H, m), 4.5l(2H, d, J=4.8Hz), 4.80(211, m), 7.15(2H, t. J=8.7Hz), 7.34(2H, m), 8.44(lH, s), 10.43(lH, s), 12.54(1H, s).
Example C-18
l-(3-Acetylamino-propyl)-5-hydroxy-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-tri aza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 177-178 °C
90

NMR (DMSO-da)S: 1.74(3H, s), 1.49-2.98(9H, m), 3.60(1H, s), 4.25-4.65(7H, m), 7.14(2H. t, J=8.4Hz), 7.34(2H, m), 7.7l(lH, s), 8.26(1H, s), 10.60(lH, s).
Example C-.19)
l-Dimethycarbamoylmethyl'5-hydroxy-6,10-dioxo'l,2]3,4,6,9>9a,10-octahydro-l,4a,8a" triaza-anthracene-7-carboxy lie acid 4-fluorcrbenzylamide
melting point: 190 °C
NMR CDMSO-do)8: 1.60(2H, m), 2.76(3H, s), 2.83(3H, s), 2.90-3.59(5H, s), 4.40(2H, m), 4,51(2H, d, 5.7Hz), 4.80(1H, d, d=14.4Hz), 4.98(1H, s), 7.16(2H, t, J=8.4Hz), 7.34(2H, m), 8.54(1H, s), 10.42(lH, s).
Example O20)
5-Hydroxy-l'(3-methanesulfonylamino-propyl)-6,10-dioxo-.l,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-cai'boxylie acid 4-fluoro-benzylamide
melting point: 176 °C
NMR (DMSO-dG)8: 1.54-1.75(4H, m). 2.80(3H, s), 2.30-3.04(8H, m), 4.45(2H, m), 4,52(2H, d, J=5.6Hz), 4.75(lH, d, J=13.2Hz), 6.91(lH, t, J=5.6Hz), 7.16(2H, t, J=8.8Hz), 7.36(2H, m), 8.6l(lH, s), 10.4l(lH, t, J=5.6H'z), 12.58(lH, .s).
Example C-21)
5-Hydroxy-2-methyl-6,10-dioxo-31416,9,9a,10-hexahydro-2H-l-oxa-4a,8a-dizazaanthia cene-7'carboxylic acid 4-fluorobenzylamide
NMR (CDC13)5: 1.27(3H, d, J=6.0Hz), 1.55-1.78(2H, m), S.IKl.H, td, J=12.9, 3.7Hz), 3.89-4.00(lH, m), 4.16(1H, dd, J=13.8, 3.9Hz), 4.34(1H, dd, J=13.8, 3.9Hz), 4.60(2H, d, J=6.0Hz), 4.7K1H, ddd, J=13.5, 48, 1.8Hz), 5.08UH, t, J=3.9Hz), 6.96-7.04(2H, m), 7.26-7.35(2H, m), 8.32(lH, s), 10.4l(lH, br s), 12.4l(lH, br s).
Example F-l)
5-Hydroxy-l-isobutyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-lH-l,3a,8a-tnazacyc3openta[b] naphthalene-7-carboxylic acid-4-fluorobenzylamide
[Chemical formula 59]
91

1) According to the method of synthesizing a compound 17-1, the crude purified product (503mg) of a compound 48 was obtained at a yield of 82% from a compound 16 <600mg).
2) To a solution of a compound 48 (iOOmg, 0.22mmol), isobutylaldehyde (39ul, 0.432mmol) and acetic acid (25ui, 0.432mmol) in dichloromethane (4ml) was added sodium triacetoxyborohydride (92mg, 0.432mmol) under ice-cooling-, and the mixture was stirred at room temperature for 2 hours. Further, isobutylaldehyde (20j.il) and sodium triacetoxyborohydride (46mg) were added, and the mixture was stirred for 30 minutes. To the reaction solution was added water, this was extracted with chloroform, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution. After driug, the solvent was distilled off under reduced pressure, and this was purified by silica gel column chromatography. A compound 49 (87mg) was obtained as a colorless crystal at a yield of 78%.
1H-NMR (CDC13)8: 0.96(3H, d, J=6.6Hz), 0.97(3H, d, J=6.3Hz), 1.72-1.86(lH, ra). 2.25-2.4.1 (2H, m), 2.47-2.58(.1H, m), 3.39-3.46(lH, m), 3.69-3.76(2H, m), 3.85-3.93(lH, m), 4.06(1H, dd, J=9.9, 2.7Hz), 4.16-4.22(1H, m), 4.57(lH, dd, J=15.3, 5.1Hz), 4.64(1H,

dd, J=14,7, 5.1Hz), 5.20(lH, d, J=9.9Hz), 5.38(1H, d, J=9.9Hz), 6.96-7.06(2H. m), 7.28-7.36(5H, m), 7.58-7.62(2H, m), 8.40(1H, s), 10.44(lH, br s).
3) According to the method of a step 17) of Example B-l, a compound l'M (43mg) was obtained at a yield of 64% from a compound 49 (81mg).
1H-NMR (DMSO-dG)6: 0.90(3H, d, J=6.4Hz), 0.91(3H. d, J=6.0Hz), 1.75-1.84(lH, m), 2.24-2.39(1H, m), 2.39-2.54(2H, m), 3.36-3.43(lH, m), 3.52-3.60(lH, m), 3.67-3.73(111, m), 3.81-3.88(1H, m), 4.19-4.23(1H, m), 4.52(2H, d, J=6.0Hz), 4,94-4.99(lH, m),
92

7.12-7.20(2H, m), 7.32-7.38(2H, in), 8.45(lH, s), 10.37(lH, t, J=2.0Hz), 11.74UH, s).
According to the same manner as that of Example F-l, the following Example compounds F-2 to F-63 were synthesized.
Example F-2)
5-Hydroxy-.l-isobutyl-6,10-dioxo-.l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting-point: 146-148 °C
1H-NMR (DMSO-de)8: 0.63(3H, d, J=6.6Hz), 0.79(3H, d, J=6.6Hz), 1.56-1.66(2H, m), 1.67-1.75(1H, m), 1.94-1.99(1H, m), 2.41-2.54(2H, m), 2.96-3.06(211, m), 4.41-4.59(5H, m), 4.76-4.8K1H, m), 7.14-7.2l(2H, in), 7.33-7.38(2H, m), 8.6l(lH, s), 10.40QH, d, J=5.8Hz), 12.56(1H, s).
Example F-3)
l-Cyclopropylmethyl-5-hydi-oxy'6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-beiizylaniide
melting point-' 182-184 °C
NMR (DMSO-d6)6: 0.06(2H, m), 0.43(2H, d, 8.4Hz), 0.80(lH, m), 1.66(2H, m), 2.28-3.30(4H, m), 4,40-4.50(4H, m), 4,52(2H, d, 6.0Hz), 4.78(2H, m), 7.15(2H, t, 8.7Hz), 7,34(2H, m), 8.55(lH, s), 10.47(lH, s), 12.55UH, s).
Example F_4)
1 - Cyclopentylme thy 1-5-hydroxy-6, l-dioxol,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 184-185 °C°C
NMR (DMSO-de)8: 0.88-2.10UH, m), 2.60(2H, m), 2.95-3.28(2H, m), 4.38"4.53(6H, m), 4.82(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.57(lH, s), 10.42(1H, s), 12.45(1H, s).
Example F-5)
5-Hydroxy l-(4-methylsulfanylbenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,.10-octahydro-l,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-dfi)S: 1.51-1.56(lH, m), 1.69-1.74(lH, m), 2.42(3H, s), 2.55-2.62(lH, m), 2.80-2.84(lH, m), 3.00"3.08(lH, m), 3.32-3.36(lH, m), 3.93(1H, d, J=13.6Hz), 4.45-4.53(4H, m), 4,58(1H, s), 4,83(lH, d, J=15.2Hz), 7.11-7.19(6H, m), 7.33-7.40(2H, m), 8.34(1H, s), 10.38(111, t, J=6.0Hz), 12.58(lH, s).
93

Example F-6)
l-(5-Chloro-l,3-dimethyllH-pyrazol-4-ylmethy])-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a, 1 Ooctahydrol,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-d6)6: 1.56-1.59(2H, m), 1.8S(3H, s), 2.37-2.45(lH, m), 2.76-2.80(lH, m), 3.00-3.06(2H, m), 3.64(3H, s), 3.87(lH, d, J=13.2Hz), 4.40-4.55(5H, m), 4.97(lH, d, J=14,4Hz), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.56(lH, s), 10.39(lH, t, J=6.0Hz), 12.46(1H, s).
Example F-7)
5-Hydroxy-l-(3-mGthoxybenzy])-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMS0-dG)5-- 1.52-1.57(1H, m), 1.70-1.80(lH, m), 2.60-2.68(lH, m), 2.84-2.90(lH, m), 3.01-3.09(1H, m), 3.36(1H, d, J=14,0Hz), 3.61(3H, s), 3.9l(lH, d, J=14.0Hz), 4.45-4.52(4H, m), 4.58(lH, s), 4.76(lH, d, J=14.8Hz), 6.68-6.73(2H, m), 6.77(lH, d, J=7.6Hz), 7,13-7.19(3H, m), 7.33-7.38(2H, m), 8.17(lH, s), 10.38(lH, t, J=6.0Hz), 12.57(111, s).
Example F"8)
5-Hydi,oxy-l-(4-me(:hanesulfonylbenzyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-dfi)S: 1.54-1.58(lH. in). 1.74-1.80(lH, m), 2.67-1.74(1H, m), 2.83-2.87(lH, m), 3.05-3.12(1H, m), 3.18(311, s), 3.52(lH, d, J=14.8Hz), 4.09(lH, d, J=14.8Hz), 4.46-4,52(4H, m), 4.67(lH, s), 4.73(.lH, d, J=14,8Hz), 7.12-7.18(2H, m), 7.32-7.36(2H, m), 7.46(2H, m), 7.80(2H, d, J=8.0Hz), 8.17(lH, s), 10.37(1H, t, J=5.8Hz), 12.59(1H, s).
Example F-9)
5-Hydroxy-l-(6-methoxypyridin-3-ylmethyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydi'O-l,4a,8a-triazaanthracene-7carboxylic acid 4-fluorobenzylamide
(DMS0-dfi)6: 1.511.56(1H, m), 1.7M.77(1H, m), 2.58-2.66(lH, m), 2.80-2.86(lH, m), 3.01-3.09(11-1, m), 3.38(1H, d, J=13.6Hz), 3.78(3H, s), 3.87(1H, d, J=13.6Hz), 4,45-4.52(4H, m), 4.60(lH, s), 4,82(lH, d, J=13.6Hz), 6.7l(lH, d, J=8.6Hz), 7.12-7.19(2H, m), 7.33-7.38(2H, m), 7.49(lH, d, J=8.6Hz), 7.98(lH, s), 8.30(lH, s), 10.37(1H, t, J=6.0Hz), 12.58QH, s).
94

Example F-lO)
5-Hydroxyl-isobutyl-3,3-dimethyl-6,.lO-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-d(i)8: 0.64(3H, d, J=6.4HzX 0.82(3H, d, J=6.8Hz), 0.90(3H, s), 0.9l(3H, s), 1.59-1.67(1H, m), 1.92-1.97(1H, m), 2.11-2.15(lH, m), 2.51-2.57(lH, m), 2.67(lPI, d, J=12.0Hz), 2,77(1H, d, J=12,8Hz), 4,13(lH, s), 4,2l(lH, d, J=12.8Hz), 4.47-4.59(3H, s), 4,80(1H, dd, J=14.4, 2.8Hz), 7.14-7.19(2H, m), 7.34-7.38(2H, ra), 8.66(lH, s), 10.4 KlH, t, J=6.0Hz), 12.44(111, s).
Example F-ll)
5-Hydroxy-l,3,3-trimethyl"6,10'dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triazaanthracene'7-carboxylic acid 4-fluorobenzylamide
(DMSO-dG)6: 0.89(6H, s), 2.14-2.18(lH, m), 2.24(311, s), 2.54-2.58(lH, m), 2.74-2.78(lH,

(DMSO-dG)6: 0.86(0H, s), 2.14-2.76(IH, m), 2.24(0H, s), 2.84-2.86(IH, m), 2.74-2.76(IH, s), 3.88(1H, s), 4.21Q.H, d, J=13.2Hz), 4.45-4.53(3H, m), 4.72-4,76(IH, m), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.64(IH, s), 10.40(IH, t, J=6.0Hz), 12.46(IH, s).

Example F-12)
4-[7-(4-Fluorobenzylcai-bamoyl)-5;hydroxy-6,10-dioxy-3,4,6,9,9a,]0-hexahydro-2H.I,4a ,8a-triazaanthracene-lyl]butanoic acid ethyl ester
(CDC13)6: 1.23(3H, t, J=7.IHz), 1.70-1.79QH, m), 1.86-2.00(1H, m), 2.17-2.34(2H, m), 2.46-2.57(IH, m), 2.61-2.77(2H, m), 2.85-2.92UH, m), 3.13-3.18(IH, m), 4.13(2H, q, J=7.1Hz), 4.27-4,34(2H, m), 4.57-4,63(3H, m), 4,66-4.73(IH, m), 6.95-7.03(2H, m), 7.29-7.36(2H, m), 8.36(IH, s), 10.48(IH, t, J=4,8Hz), 12.50(.1H, s).
Example F-13)
1-(3-Dime thy lcarbamoylp ropy 1)-5-hydroxy-6,10-dioxo-1,2,3,4,6,91,10-08 hydro-1,4a, 8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(CDCl3)8:i.62-1.82(3H, m), 1.83-2.00(.1H, m), 2.10-2.35(2H, m), 2.57-2.65(2H, m), 2.75-2.95(2H, m), 2.92(3H, s), 2.96(3H, s), 3.07-3.140.H, m), 4,23-4,30(2H, m), 4.60(2H, d, J=6.0Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 5.12(IH, d, J=12.6Hz), 6.95-7.02(2H, m), 7.28-7.35(2H, m), 8.42(IH, s), 1054O.H, t, J=5.4Hz), 12.5K1H, s).
Example F-14)
5-Hydroxy-l-(4-morpholin-4-yl-4-oxobut.yl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a ,8a-triazaanthracene-7 carboxylie acid 4-fluorobenzylamide
95

(CDCWS: l.Gl-1.83(3H, m), 1.84-2.00UH, m), 2.12-2.23(IH, m), 2.25-2.360.H, m), 2.56-2.64(2H, in), 2.75-2.95(2H, m), 3.09-3.15(1H, ra), 3.37(2H, t, J=4.8Hz), 3.61-3.66(6H, m), 4.26-4,32(2H, m), 4,59(2H, d, J=5.7Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 4.95-5.01(1H, in), 6.957.03(211, m), 7.28-7.35(2H, m), 8.40(IH, s), 10.52(IH, t, J=5.7Hz), 12.51(1H, s).
Example F-15)
5-Hydro xy-l-methyl-6J.0-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l ,4a,8a-triazaanthracene-7-carboxylie acid 4-fluorobenzylamide
melting point: 252-253°C
(DMSO-dc)8: 1.56-1.75(2H, ra), 2.22(3H, s), 2.50"2.55(1H, m), 2.90-3.10(2H, m), 4.17(1H, brs), 4.39-4,42(2H, m), 4.52(2H, d, J=6.0Hz), 4,74-4.78(IH, m), 7.13"7.17(2H, m), 7.33-7.37(2H, m), 8.6I(IH, s), 10.40(IH, t, J=6.0Hz), 12.54(IH, s).
Example F-16)
5-Hydroxy-6,10-dioxol-thiophen-3-ylmethyl-l,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaz aanthracene-7-carboxylic acid 4-fhiorobenzylamide
melting point-' 242-243°C
(DMSO-ds)6: 1.52-1.73(2H, m), 2.5>2.62(IH, m), 2.87-3.03(2H, m), 3.52(1H, d, J= 13.6Hz), 3.90(1H, d, J=14.4Hz), 4.40-4.56(51-1, m), 4.83-4.90(IH, m), 6.92(1H, d, J=5.2Hz), 7.13-7.17(2H, m), 7.28-7.37(3H, m), 7.42-7.44(IH, m), 8.46(IH, s), 10.39(111, t, J=6.0Hz), 12.58(1H, s).
Example F-17)
5-Hydroxy-6,10-dioxo-l-thiazol-2-ylmethyl-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-tnazaa nthracene'7-carboxylic acid 4-fluorobenzylamide
melting point 214-215°C
(DMSO-de)8: 1.54-1.72(2H, m), 2.75-2.81(1H, m), 2.95"3.07(2H, m), 3.80(1H, d, J=16.0Hz), 4,37(1H, d, J=16.4Hz), 4.44-4.5K4H, ra), 4.69(IH, brs), 4,89-4.93(111, m), 7.13-7.17(2H, m), 7.32-7.35(2H, m), 7.55(IH, d, J=3.2Hz), 7.69(1H, d, J=3.2Hz), 8.37(1H, s), 10.36(1H, t, J=6.0Hz), 12.50(IH, s).
Example F-18)
5-Hydroxy-(3-methylsulfanyl-pi-opyl)-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-tr iazaanthracene-7-carboxylic acid 4-fluorobenzylamide
96

melting point: 162-1G4°C
(DMSOdti)S' 1.50-1.82(4H, m), 2.27(3H, s), 2.32-2.44(3H, in), 2.60-2.82(2H, m), 3.00-3.14(2H, m), 4.37-4.59(5H, m), 4.75"4.79(IHf m), 7.13-7.17(21-1, in), 7.33-7.35(2H, m), 8.60(1H, s), 10.40(IH, t, J=6.0Hz), 12.57(1H, s).
Example F-19)
5-Hydroxy-6,10-dioxo-l-pyridin-4-ylmethyl- l,2,3,4,C>,9,9a,10octahydro-l,4a,8a-triazaa nthi-acene-7carboxylic acid 4-fluorobenzylamide
melting point: 180"183°C
(DMSO-dG)5: 1.52-1.76(2H, m), 2.62-2.80(2H, m), 3.01-3.07(IH, m), 3.42(1H, d, J=15.2Hz), 4.05(1H, d, J=15.2Hz), 4.49-4.50(4H, m), 4.64(IH, brs), 4.78"4,8I(IH, m), 7.12-7.21(4H, m), 7.32-7.36(2H, m), 8.33(1H, s), 8.42(2H, d, J=4.4Hz), 10.39(IH, t, J=6.0Hz). 12.55(1H, s).
Example F-20)
l-Cyclohexylmethyl-5hydroxy-6, lOdioxo-] ,2,3,4,6,9,9a, lOoctahydro'1,4a,8atriazaan thracene-7-carboxylic acid 4-fluorobonzylaimde
melting point: 201-202°C
(DMSO-d6)6: 0.56"0.59(IH, m), 0.870.84(IH, m), 1.02-1.13(3H, m), J.231.290H, m), 1.49-1.70(6H, m), 1.92-L97(IH, m), 2.52-2.550.H, m), 2.96"3.03(2H, m), 4,40-4.43(3H, m), 4.52(2H, d, J=6.0Hz), 4.73-4.77(11-1, m), 7.12-7.16(2H, m), 7.32-7.36(2H, m), 8.590H, s), 10.40(1H, t, J=5.2Hz), 12.58(1H, s).
Example F"21.)
5-Hydroxy-6,10-dioxo-l-pyridin-2-ylmethyl-l,2,3,4,6,9,9a, 10-octahydrol,4a,8a-triazaa nthracene-7-carboxylic acid 4fluorobenzylamide
molting- point: 216"219CC
(DMSO-dG)5: 1.52-1.76(2H, in), 2.66-2.80(IH, m), 2.90-3.07(2H, m), 3.67(IH, d, J=I5.2Hz), 4.01(1H, d, J=13.2Hz), 4,37-4.97(4H, m), 4.62(IH, brs), 4.85-4.88(I.H, m), 7.07-7.25(41-1, m), 7.33"7.36(2H, in), 7.64--7.68(IH, m), 8.26(1H, s), 8.45(IH, s), 10.36(1H, t, J=6.0Hz), 12.57(1H, s).
Example F-22)
l-(2-E(;hyl-butyl)-5-hyd1oxy-6,10-dioxo-l,213,4,6,9,9a,10-octahydro-l,4a,8a-triazaanthr acene-7-carboxylic acid 4fluorobenzylamide

97

melting-point: 137-140°C
(DMSOdfi)8: 0.62(3H, t, J=7.2Hz), 0.77(3H, t, J=7.2Hz), 0.99-1.30(5H, m), 1.57-1.71(2H, m), 1.97-2.02(lH, m), 2.44-2.58(2H, m), 3.02-3.32(2H, m), 4.34-4.57(5H, m), 4.78-4.820.H, m), 7.13-7.17(2H, m), 7.32-7.36(2H, m), 8.60(1H, s), 10.39(1H, t, J=5.2Hz), 12.54(1H, s).
Example F-23)
5-Hydroxy-l-(2-morpholin-4-ylethyl)-6,10-dioxo- 1,2,3,4,6,9,9a, 10-octahydrcrl, 4a, Satri azaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting-point: 254-256°C
(DMSO-da)S: 1.55-1.68{2H, m), 2.28-2.39(8H, m), 2.59-2.65(lH, m), 2.82-3.09(3H, m), 3.33-3.58(5H, m), 4,34-4,50(3H, m), 4.52(2H, d, J=5.2Hz), 4.79-4.84(l.H, m), 7.12-7.17(2H, m), 7.32-7.36(2H, m), 8.52(1H, s), 10.45(lH, t, J=5.2Hz), 12.55(lH, s).
Example F-24)
l-Hydroxy-6-methyl-2,ll-dioxo-2,5a,6,7,8,9,10,ll-octahydro-5H'4a,6, lOatriazacycloh epta(b]napbthalene-3-carboxylic acid 4-fluorobenzylamide
melting point: 255°C
(DMSO-dG)6: 1.48-1.55(lH, m), 1.67-1.80(3H, m), 2.29(3H, s), 2.75-2.80(2H, m), 3.23-3.31(1H, m), 4.07"4.09(lli, m), 4,36-4.40(1H, m), 4.45-4.59(3H, m), 4,68-4,69(lH, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.50(lH, s), 10.42(lH, t, J=6.0Hz), 12.42(1H, s).
Example F-25)
.l-Hydroxy-6-isobu(.yl-2,ll-dioxo-2,5a,6,7,8,9,10,ll-octahydro-5H-4a,6,10a-triaza-cyclo hepta[bJnaphthalene-3-carboxylic acid 4-fluorobenzj'lamide
melting-point: 221-223°C
DMSO-d)8: 0.8l(3H, d, J=6.8Hz), 0.84(3H, d, J=6.4Hz), 1.45- 1.78(5H, m), 2.36-2.54(2H, m), 2.27-2.93(2H, m), 3.17-3.23(lH, m), 4.03-4.06(lH, m), 4,32-4,56(4H, m), 4.82-4.85(lH, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.48(lH, s), 10.42(1H, t, J=6.0Hz), 12.53(1H, s).
Example F-26)
6-Cyclopropylmethyl-.l-hydroxy-2,ll-dioxo-2,5a,6,7,8,9,10,ll-octaliydro-5H-4a,6,10a-tr iaza-cyclohepta[b]naphthaleiie-3-carboxylic acid 4-fluorobenzylamide
98

melting point- 213°C
DMSO-dG)6: 0.15-0.26(21-1, rn), 0.46-0.48(2H, m), 0.86-.l.06(lH, m), 1.45-1.75(4H, m), 2.45-2.65(lH, m), 2.68-2.83(lH, m), 2.91-2.98(2H, m), 3.17-3.26(1H, m), 4.08-4.14(1H, m), 4.43-4.45(2H, m), 4.54(2H, d, J=5.6Hz), 4.89-4.9l(lH, m), 7.15-7.19(2H, in), 7.35-7.39(2H, m), 8.50(lH, s), 10.47(lH, t, J=6.0Hz), 12.52(lH, s).
Example F-27)
l-Furan-2-ylmethyl-5-hydi.oxy-6,10 dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-a nthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 193-197°C
DMSO-de)6: 1.67(2H. m), 2.6l(lH, s), 2.93(2H, m), 3.75(1H, d, J=14.8Hz), 3.84(1H, d, J=14.8Hz), 4.34-4.47(3H, m), 4.52(2H, d, J=6.0Hz), 4.96(1H. d, J=14.8Hz), 6.36(2H, s), 7.16(2H, t, J=8.8Hz), 7.35(2H, m), 7.59(lH, s), 8.97(lH, s), 10.43(lH, s), 12.5l(lH, s).
Example F-28)
l-(4"Dimethylamino-benzyl)-5-hydroxy-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylie acid 4-fluorobenzylamide
melting-point: 221-223°C
DMSO-dc)6-- 1.55-1.99(2H, m), 2.87(6H, s), 2.87-3.06(4H, m), 3.80(1H, d, J=14-0Hz), 4.50(5H, m), 4,83(lH, d, J=14,0Hz), 6.58(2H, d, J=9.6Hz), 6.98(2H, d, J=8.8Hz), 7.15(211, t, J=8.8Hz), 7.35(2H, m), 8.3l(lH, s), 10.39(1H, s), 12.58(lH, s).
Example F-29)
5-Hydroxy-6,10-dioxo-l-(4-trifluoromethyl-benzyl)-1,2,3,4,6,9,9a, 10-octahydro-1,4a, 8a-ti-iaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 273-277°C
DMSO-da)6-: 1.52-1.70(2H, in), 2.63-3.04(3H, m), 3.50(lH, d, J=14.8Hz), 4,10(lH, d, J=14.8Hz), 4.54(5H, m), 4.79(1H, d, J=14.8Hz), 7.14(2H, t, J=8.8Hz), 7.33(2H, m), 7.55(2H, d, J=6.8Hz), 7.6l(2H, d, J=8.0Hz), 8.22(1H, s), 10.40(1H, s), 12.56(lH, s).
Example F30)
5-Hydroxy 6,10-dioxo-l-pyridin-3-ylmethyl-1,2,3,4,6,9,9a, 10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 210-212°C
DMSO-dc)8: 1.51-1.76(2H, m), 2.63(lH, t, J=12.8Hz), 2.80(lH, d, J=12.0Hz), 3.07(lH, t,
99

J=12.8Hz), 3.44(1H, d, J=13.2Hz), 4.00(lH, d, 14.0Hz), 4.47(4H, m), 4.62(1H, s), 4.84(lH, d, J=14.0Hz), 7.16(2H, t, J=8.8Hz), 7.33(2H. m), 7.58(1H, d, J=7.6Hz), 8.30(1H, s), 8.45(2H, s), 10.4l(lH, s), 12.57(1H, s).
Example F-3l)
1-(2-Chloro-6-fluoro-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-1,4a,8a-triaza'anthracene'7-carboxylic acid 4-fluorobenzylamide
melting point: 213-215°C
DMSO-da)6:i.58(2H, 2Hl), 2.55-3.09(3H, m), 3.45(lH, d, J=12.4Hz), 4.16(1H, d, J=12.4Hz), 4.40-4,58(41-1, m), 5.12(111, d, J=14.4Hz). 7.15-7.38(7H, m), 8.66(lH, s), 10.41(1H, t, J=6.4Hz), 12.46(1H, s).
Example F-32)
5-Hyd roxyl-(4-me thoxy benzyl)-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-1,4a,8a-triaza-antliracene-7-carboxylic acid 4"fluorobenzylamide
melting point: 191193°C
NMR (DMSO-de)6:l.50-1.77(2H, m), 2.58-3.06(3H, m), 3.68(3.H, s), 3.88(lH, d, J=13.6Hz), 4,41-4.55(4H, m), 4,80(2H, d, J=14.4Hz), 6.80(2H, d, J=8.8Hz), 7.09(2H, d, J=8.4Hz), 7.15(2H, t, J=8.8Hz), 7,35(2H, m), 8.28(lH, s), 10.48(1H, s), 12.58(lH, s).
Example F-33)

Example F-33)
l-(3,5-Bis-trifluoromethyl-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydi-o-l, 4a,8a-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 275-277°C
NMR (DMSO-de)8:i.58-1.88(2H, m), 2.51-3.14(3H, m), 3.33-4.10(3H, m), 4.5l(2H, m), 4,73(1H, m), 7.15(2H, m), 7.34(2H, m), 7.82-7.93(4li, m), 10.3l(IH, s), 12.57(IH, s).
Example F-34)
l-(4-Diethylamino-benzyl)-5-hydroxy-6,10-dioxo-.l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 182°C
NMR (DMS0-dfi)8: 1.04(6H, t, J=6.8Hz), 1.50-1.69(2H, m), 2.55'3.05(3H, m), 3.26(4H, q, J=7.2Hz), 3.80(1H, d, J=13.6Hz), 4.44-4.57(4H, m), 4.9l(IH, d, J=12.4Hz), 6.52(2H, d, J=8.8Hz), 6.94(211, d, J=8.4Hz), 7.15(2H, t, J=8.4Hz), 7.35(2H, m), 8.46(IH, s), 10.4K1H, s), 12.60(1H, s).
100

Example F-35)
5-Hydroxyl-((E)-2-methyl-but-2-enyl)-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l.4a.8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 175-177°C
NMR (DMS0-dG)5: 1.35(3H, s), 1.51(3H, d, J=6.0Hz), 1.52-1.69(3H, m), 2.60-3.15(3H, m), 4,31-4.52(5H, m), 4.67-4.76(IH, m), 5.30-5.40{IH, m), 7.15(2H, t, J=8.4Hz), 7.28-43(21-1, m), 8.46(IH, s), 10.39(1H, brs), 12.60(1H, s).
Example F-36)
l-(3-Dimethylamino-2-methyl-propyl)-5-hydroxy-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthraceiie-7-carboxylic acid 4-fluoro-benzylamide
NMR (DMS0-de)8: 0.63-0.68(2H, m), 1.57-1.82(3H, m), 2.11-2.49(10H, m), 2.98-3.ll(2H, m), 4.41-4.54<5H, m), 4.73-4.80(IH, m), 7.14-7.18(2H, m), 7.31-7.38(2H, m), 8.58(1H, s), 10.40QH, s), 12.57(IH, s).
Example F-37)
l-(3,3-Dimethyl-butyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 175-177°C
NMR (DMS0-de)6: 1.19-1.36(2H, m), 1.57-1.70<2H, m), 2.23-2.30(1H, m), 2.51-2.69(2H, m), 2.97-3.04(2H, m), 4.42-4.54(5H, m), 4.78(IH, d, J=14.0Hz), 7.13-7.17(2H, m), 7.33-7.36(2H, m), 8.63(IH, s), 10,39(IH, t, J=6.0Hz), 12.56(1H, s).
Example F-38)
l-Ethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 221°C
NMR (DMS0-de)8: 0.94(3H, t, J=6.8Hz), 1.56-JL.7l(2H, in), 2.45-2.50(IH, m), 2.59-2.76(2H, m), 2.96-3.03(2H, rtf), 4.40-4.44(3H, m), 4.52(2H, d, J=6.0Hz), 4.77-4,82(IH, m), 7.14-7.18(2H. m), 7.34-7.38(2H, m), 8.62(IH, s), 10.4l(IH, t, J=6.0Hz), 12.59(1H, s).
Example F-39)
5'Hydroxy-6,10-dioxo-l-(2-oxo-propyl)-1,2,3,4,6,9,9a,.10-octahydro-1,4a,8a-triaza-anth
101

racene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 244-246°C
NMR (DMSO-do)8: 1.54-1.6l(IH, m), 1.67-1.76QH, m), 2.22(3H, s), 2.50-2.56(IH, m), 2.91-3.02(2H, m), 4.18(IH, s), 4.38-4.45(2H, m), 4.52(2H, d, J=6.0Hz), 4.76(IH, d, J = 14,4Hz). 7.13-7.18(2H, m), 7.34-7.37(2H, m), 8.6l(IH, s), J.0.40(IH, t, J=G.0Hz), 12.54(1H, s).
Example F-40)
5-Hydroxy-6,10-dioxo-l-(4,4,4-trifluorobutyD-1,2,3,4,6,9,9a, lOoctahydro-1,4a,Satriaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 220°C
NMR (DMSO-ds)6: 1.53-1.62(2H, m), 1.67-1.75(IH, m), 2.07-2.18(2H, m), 2.40-2.47(IH, m), 2.64-2.78(2H, m), 2.96-3.04(2H, m), 4.42-4,49(2H, m), 4.53(2H, d, J=5.2Hz), 4.74(1H, d, J=12.8Hz), 7.13-7.17(2H, m), 7.33-7.37(2H, m), 8.6l(IH, s), 10.40UH, t, J=6.0Hz), 12.57C1H, s).
Example F-4l.)
5-Hydroxy-l-(3-methyl-butyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro- l,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 151°C
NMR (DMvSO-dB)6: 0.78(6H, dd,J=7.6, 16.2Hz), 1.2M.28(2H, m), 1.41-1.48(IH, m), 1.56-1.71(2H, m), 2.22-2.3l(IH, m), 2.51-2.59UH, m), 2.66-2.73(IH, m), 2.96-3.05(2H, m), 4,41-4.55(5H, m), 4,80(IH, d,"J=13.2Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8.64(1H, s), 10.40(111, t, J=6.0Hz), 12.57(1H, s).
Example F-42)
5-Hydroxy-l-isobutyl-6,10-dioxo-l,2,3,4,6,9,9a,.IO-octahydro-l,4a,8atriaza-anthracene-7-carboxylic acid 3chloro-2-fluorobenzylamide
melting-point: 180-.182°C
NMR (DMSO-dc)6: 0.62(3H, d, J=6.0Hz), 0.78(3H, d, J=6.4Hz), 1.55-1.69(3H, m), 1.93-1.99(1H, m), 2.97-3.08(2H, m), 4.39-4.46(3H, in), 4.59-4.64(2H, m), 4.75-4.8l(IH. m), 7.16-7.23(1H, m), 7.27-7.34(IH, m), 7.47-7.53(.IH, m), 8.59(IH, s), 10.44(IH, s), 12.67(1H, s).
Example F-43)
102

l-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-l,2,3,4,6,9,9a,10'Octahydro-l,4a,8a-triaza-anthracene 7-carboxylic acid 3chloro-2-fluoro-benzylamide
melting point-' 189-192°C
NMR (DMSO-dR)S: 0.00-0.10(2H, m), 0.35-0.4l(2H, m), 0.70-0.77(IH, m), 1.57-1.69(2H, m), 2.52-2.65(1H, in), 2.67-2.85(IH, m), 2.91-2.99UH, m), 4.30-4.4l(2H, m),

4.48-4,52(2H, m), 4.71-4,80(IH, m), 7.06-7.10(IH, m), 7.18-7.22(IH, m), 7.36-7.40(IH, m), 8.52(.1H, s), 10.30(IH, s), 12.26(IH, s).

Example F44)

l-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-tria7-aanthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 190-192°C

NMR (DMSO-d6)S: 1.56-1.68(2H, m), 2.54-2.63(IH, m), 2.89-2.99(2H, m), 3.80(2H, dd, J=18.4, 33.2Hz), 4,37-4,5l(3H, m), 4.62(2H, d, J=6.0Hz), 4,97(IH, d, J=15.2Hz), 6.39(2H, s), 7.18-7.22(11-1, m), 7.31-7.34(1H, in), 7.48-7.5l(lli, m), 7.58(IH, s), 8.64(1H, s), 10.45(1H, t, J=6.0Hz), 12.55(IH, s).

Example F-45)

5-Hydroxy-6,10-dioxo-.l-thiazol-2-ylmethyl-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7 carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 217"219°C

NMR (DMSO-d(i)6: 1.59-1-74(2H, m), 2.76-2.83(IH, m), 2.97-3.08(2H, m), 3.90(IH, d, J=16.0Hz), 4.36(1H, d, J=16.0Hz), 4,45-4.69(51-1, m), 4,89(1H, d, J=14.8Hz), 7.18-7.22(1H, m), 7.28-7.3l(IH, m), 7.47-7.53(IH, m), 7.54(IH, d, J=3.2Hz), 7.68(1H, d, J=3.2Hz), 8.34(1H, s), 10.40(IH, d, J=6.0Hz), 12.52(l.H, s).

Example F46)

5-Hydroxy-6,10-dioxo-lpyridin-2-ylmethyl-1,2,3,4,6,9,9a, 10-octahydro-l, 4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 190-193°C

NMR (DMS0-do)6: 1.541.6K1H, m), 1.691.75(111, m), 2.66-2.74(IH, m), 2.91-3.08(2H, m), 3.68(1H, d, J=14.4Hz), 4.02Q.H, d, J=14.8Hz), 4.40-4.67(5H, m), 4,85(IH, d, J=12.4Hz), 7.16-7.35(3H, m), 7.46-7.52QH, m), 7.61-7.69(IH, m), 8.20(IH, s), 8.43-8.47(11-1, m), 10.4K.1H, d, J=6.0Hz), 12.58(111, s).

103

Example F-47)

5-Hydroxy-l-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-anthracene-7-carbox3']ic acid 2,4difluoro-benzylamide

melting point: 194°C

NMR (DMSO-d6)6: 0.62(3H, d, J=6.4Hz), 0.78(3H, d, J=6.4Hz), 1.55-1.69(3H, m), 1.93-1.99(11-1, m), 2.97-3.08(2H, m), 4.39-4.46(311, m), 4.50-4.59(2H, m), 4.770.H, d, J=14.4Hz), 7.03-7.09(IH, m), 7.20-7.280.H, m), 7.36-7.430H, m), 8.59(1H, s), 10.39(1H, s), 12.56(111, s).

Example F-48)

l-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-l,2)3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 169'-171°C

NMR (DMSO-d6)8: 0.00-0.10(2H, m), 0.42-0.44(2H, m), 0.77-0.8l(IH, m), 1.59-1.74(2H, m), 2.27-2.32(IH, m), 2.62-2.72UH, m), 3.05-3.12(1H, m), 4.30-4.58(5H, m), 4,G9(IH, d, J=14.8Hz), 7.03-7.1l(IH, m), 7.22-7.26QH, m), 7.37-7.40UH, in), 8.62(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(IH, s).

Example F-49)

l-Furan-2ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9 a, 10-octahydro-l,4a,8atriaza-anthracene-7'carboxylic acid 2,4-difluoro-benzylamide

melting-point: 186-188°C

NMR (DMSO-ds)6: 1.55-1.68(2H, m). 2.55-2.64(111, m), 2.88-2.99(2H, m), 3.80(2H, dd, J=15.6, 34.8Hz), 4.36-4.56(5H, m), 4.97(IH, d, J=16.0Hz), 6.39(2H, s), 7.05-7.08(IH. m), 7.21-7.26(1H, m), 7.37-7.44(IH, m), 7.58(IH, s), 8.64(IH, s), 10.38(IH, t, J=5.6Hz), 12.53(1H, s).

Example F-50)

5-Hydroxy-6,10-dioxo-l-thiazol-2-ylmethyl-l,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 168-170°C

NMR (DMSO-dc)6: 1.59-1.74(2H, m), 2.76-2.83(IH, m), 2.97-3.08(2H, m), 3.89(IH, d, J=16.4Hz), 4.36(1H, d, J=16.0Hz), 4.44-4.55(4H, m), 4.69(IH, s), 4.89(1H, d, J=14.8Hz), 7.03-7.09(IH, m), 7.20-7.27(IH, m), 7.34-7.4l(IH, m), 7.54(IH, d, J=3.2Hz). 7.68(1H, d, J=3.2Hz), 8.34(IH, s), 10.35(IH, d, J=6.0Hz), 12.50(1H, s).

104

Example F-51)

5-Hydroxy-6,10-dioxo-l-pyridin-2-ylmethyM,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 200-203°C

NMR (DMS0-dB)6: L54-1.6K.1H, m), 1.69-1.780LH, m), 2.7.1-2.79(111, m), 2.91-3.09 (2H, m), 3.72(1H, d, J= 14.4Hz), 4.07(IH, d, J=14,4Hz), 4.44-4.54(4H, m), 4.70(1H, s), 4,82(111, d, J=14.4Hz), 7.04-7.10(1H, m), 7.2J -7.42(4H, m), 7.74-7.800.H, m), 8.17(IH. s), 8.47-8.49(IH, m), 10.35(1H, d, J=6.0Hz), 1.2.57(l.H, s).

Example F-52)

l-H'ydroxy-6-methyl-2, ll-dioxo-2,5a,6,7,8,9,10, ll-octahydro-5H-4a,6,10a-triaza-cycloheptа[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 230-231°C

NMR (DMSO-do)8: 1.47-1.53(1H. m), 1.62-1.78(3H, in), 2.29(3H, s), 2.77-2.81 (2H, m), 4.05-4.10(1H, in), 4,35-4.40(IH, m), 4.54-4.64(3H, m), 4,70(1H, s), 7.18-7.22(IH, m), 7.30-7.34-UH, m), 7.47-7.52(IH, m), 8.49(111, s), 10.47(1H, d, J=6.0Hz), 12.44(IH, s).

Example F-53)

l-Hydroxy-6-isobutyl-2,ll-dioxo-2,5a,6,7,8,9,10,ll-octahydi-o-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 215-216°C

NMR (DMS0-de)6: 0.83(6H, dd, J=6.8, 13.6Hz), 1.45-1.80(5H, m), 2.36-2.41(IH, m), 2.77-2.93(2H, m), 3.17-3.240.H, m), 4.02-4,09(IH, m), 4,32-4.40(211, m), 4.6l(2H, d, J=5.6Hz), 4.82-4.84(IH, m), 7.18-7.22(1H, m), 7.30-7.33(IH, m), 7.48-7.5l(IH, m), 8.47(1H, s), 10.48(1H, t, J=6.0Hz), 12.55(IH, s).

Example F-54)
6-Cyclopropylmethyl-l-hydioxy-2,ll-dioxo-2,5a,6,7,8,9,10,.ll-octahydro-5H-4a,6,10a-ti:
iaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point-' 212°C
NMR (DMSO-ds)8: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(lH, m), 1.45-1.77(3H,
m), 2.64-2.69(l.H, m), 2.85-2.95(2H, in), 3.13-3.20(1H, m), 4.03"4.09(lH, m),
4.36-4.40(2H, m), 4.59(2H, d, J=5.6Hz), 4.84-4.86(lH, m), 7.16-7.20(111, m),
7.28-7.32(1H, m), 7.46-7.50(lH, m), 8.45(lH, s), 10.460H, t, J=6.0Hz), 12.50(lH, s).
105

Example F'55)
6-Fuian-2-y]methyM-hydroxy-2,ll-dioxo-2,5a,617,8,9,.l0,ll-octahydro-5H-4a,6)l0a-tri
aza-cyclohepta[b]naphthalene'3-carboxylic acid 3-chloro-2-fluoro-benzylamide
Melting point: 189-190°C
NMR (DMSO-'do)6: 1.48-1.63(3H, m), 1.70-1.77(lH, m), 2.79-2.83(2H, m). 3.90(2H. dd,
J=14,8, 39.6Hz), 4.05-4.11(1H, m), 4.40-4,5l(2H, m), 4,6l(2H, d, J=5.6Hz),
4.89-4.9K1H, m), 6.30-6.33(lH, m), 6.38-6.40(lH, m), 7.18-7.22Q.H, m), 7.30-7.34(lH,
m), 7.48-7.53(1H, m), 7.57(l.H, s), 8.45(lH, s), 10.45(lH, t, J=6.0Hz), 12.44-(lH, s).
Example F-56)
l-Hydroxy-6-Tnethyl-2,ll-dioxo-2,5a,6,7,8,9,10,ll-octahydro-5H-4a,6,10a-triaza-cycloh
eptafbjnaphthalene-3-carboxylic acid 2,4-diiluoro-benzylamide
melting point: 241°C
NMR (DMSO-da)S: 1.47-1.53(1H, m), 1.62-1.78(3H, m), 2.29(3H, s). 2.77-2.81 (2H, m),
4,05-4.10(1H, m), 4,35-4.40(lH, m), 4.53-4,6l(3H, m), 4,69(lH, s), 7.03"7.08(lH, m),
7.20-7.27(11-1, m), 7.37-7.43(1H, m), 8.49(lH, s), 10.42(lH, d, J=6.0Hz), 12.43UH, s).
Example F-57)
l.-Hydroxy-6-isobutyl-2, ll-dioxo-2,5a,6l7,819,101ll-octahydro-5H-4a,6110a-triaza-cyclo
hepta[b]naphthalene"3 carboxylie acid 2,4difluoi'0-benzylainide
melting point: 203°C
NMR (DMSO-d6)6: 0.82(6H, dd, J=6.4, 13.2Hz), 1.45-1.80(5H, m), 2.36-2.42(lH, in),
2.77-2.93(2H, m), 3.15-3.23(lH, m), 4,02-4,08(lH, m), 4,32-4.4 l(2H, m), 4.54(2H, d,
J=5.6Hz), 4,82-4,84(lH, m), 7.02-7.09(lH, m), 7.20-7.27(lH, m), 7.36-7.43(lH, m),
8.47(1H, s), 10.4-KlH, t, J=6.0Hz), 12.54(lH, s).
Example F-58)
6-Cyclopropyhnethyl-l-hydroxy-2,ll-dioxo-215a,6,7,8,9,10,ll-octahydi-o-5H-4a,6,10a-tr
iaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide
melting point: 182-183°C
NMR (DMSO-de)8: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(1H, m), 1.43:1.77(3H,
m), 2.60-2.69(111, m), 2.85-2.95(2H, m), 3.11-3.19(lH, m), 4.00-4.06(lH, m),
4.36-4.40(21-1, m), 4,51 (211, d, J=5.6Hz), 4.83"4.87(1H, m), 7.00-7.07(lH, m),
7.16-7.23(1H, m), 7.34--7.38(lH, m), 8.44(lH, a), 10.39UH, t, J=6.0H.z), 12.47(lH, s).
106

Example F-59)
e-Furan-ylmethyM-hydroxy.ll-dioxo.Ga.G.T.S.O.lO.ll-octahydro-SHa.e, lOa-tri
aza-cyclohepta[b]naphthalene-3-carboxylie acid 2,4-difluorcrbenzylamide
melting point: 17M73°C
NMR (DMSO-dG)6: 1.47-1.64(3H, m), 1.70-1.77(lH, m), 2.79-2.83(2H, m), 3.90(2H, dd,
J=15.6, 39.6Hz), 4.05-4.11(1H, m), 4.41-4.57(4H, m), 4.90-4.92(lH, in), 6.30-6.33C.lH,
m), 6.38-6.40(lH, m), 7.03-7.09(lH, m), 7.20-7.27(lH, m), 7.37-7.45(lH, m). 7.57(lH,
s), 8.44(11-1, s), 10.41UH, t, J=6.0Hz), 12.43(lH, s).
Example F-60)
5-Hydroxy-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a'diaza-anthracene-7-car
boxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 276°C
NMR (DMSO-dG)6: 1.60-1.68(lH, in), 1.77-1.84(lH, m), 3.85-3.93 (1H, m),
4,03-4.07(lH, m), 4,43-4,62(5H, m), 5.28(lH, s), 7.17-7.22(lH, in), 7.29-7.34(lH, m),
7.47-7.52(lH, m), 8.49(1H, s), 10.4K1H, d, J=6.0Hz). 12.48(lH, s).
Example F"61)
5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H' l-oxa-4a,8adiaza-anthracene-7-car
boxylic acid 2,4'difluoro-benzylamide
melting point: 258°C
NMR (DMSO-dfi)6: 1.60.1.69(l.H, m), 1.77-1.85(lH, m), 3.86-3.92 (lH, m).
4.04-4.08(lH, m), 4.43-4.55(5H, m), 5.28(lH, s), 7.03-7.09(lH, m), 7.21-7.27(lH, m),
7.36-7.43(1H, m), 8.50(lH, s), 10.35(lH, d, J=6.0Hz), 12.47(lH, s).
Example F-62)
5-Hydroxy-l-(2-methoxy-ethyl)-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydrol,4a,8a-triaza-a
nthracene-7carboxylic acid 3-chloro-2-iluorobenzylamide
melting point: l93°C
NMR (DMSO-do)S: 1.53-1.73(2H, m), 2.51-2.58(1H, m), 2.71-2.78(lH, m), 2.81.-2.87
(1H, m), 2.95-3.08(2H, m), 3.17(3H, s), 4.40-4.52(3H, m), 4.62(lH, d, J=5.6Hz),
4,78(1H, d, J=14.4Hz), 7.18-7.22(1H, m), 7.30-7.34(111, m), 7.47-7.52(lH, in), 8.55(lH,
s), 10.45(1H, d, J=6.0Hz), 12.59(lH, s).
107

Example F-63)
5-Hydroxyl-(2-methoxy-ethyl)-6110-clioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triaza-a
nthracene'7-carboxylic acid 2,4'difluorcrbenzylamide
melting" point: 166-168°C
NMR (DMSO-do)8: 1.55-1.72(2H, m), 2.51-2.58(1H, m), 2.70-2.77(lH, m), 2.80-2.87
(1H, m), 2.97-3.07(21-1, m), 3.18(3H. s), 4.39-4.52(3H, m), 4.54(lH, d, J=5.2Hz),
4.78(1H, d, J=13.6Hz), 7.03-7.O9(lH, m). 7.20-7.27(lH, m), 7.37-7.43(lH, m), 8.55(lH,
s), 10.40(111, d, J=6.0Hz), 12.58(1H, s).
Example P-64)
5-Hydroxy-l-(IH-imidazol-4-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a, 10-octahydro-l,4a,8a-t
riazaanthracene-7-carboxylic acid 4-fluorobenzylamide

hazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-dfi)S: 1.55-1.59(IH, m), 1.64-1.70(1H, m), 2.58-2.66(IH, m), 2.87-2.95(2H, m), 3.67(1H, d, J=15.2Hz), 3.73(1H, d, J=15.2Hz), 4.34(IH, s), 4,38-4.43(111, m), 4.47-4.54(3H, m), 5.05(IH, d. J=14.0Hz), 7.00(1H, s), 7.13"7.19(2H, m), 7.33-7.38(IH, m), 7.59(Ili, s), S.55(IH, s), 10.4l(Ili, t, J=5.6Hz), 11.95(1H, br s), 12.59(IH, s).
Example Hi)
l-Acety]-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a'hexahydrolH- l,3a,8a-triaza-cyclopenta(b]n aphthalene-7-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 6l)

l) To a solution of a compound 48 (l20mg, 0.26 mraol) in methylene chloride (1.2 ml) were added triethylamine (43 pi, 0.31 mraol), acetic anhydride (29 j.il, 0.31 mmol), and 4-dimethylaminopyiidine (cat.) at"room temperature, and the mixture was stirred for 30 minutes. Further, triethylamine (18 ul, 0.13 mmol) and acetic anhydride (12 pi, 0.13 mmol) were added, and the mixture was stirred for 4 hours. 2N hydrochloric
1.08

acid was added, this was extracted with chloroform, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure. Diisopropyl ether was added to crystallize the material, which was filtered to obtain 53 (112 mg) as a pale orange crystal at a yield of 86 %.
2) An Example compound H'l (71 mg) was obtained at a yield of 82 % from a compound 53 (106 mg), according to the method of Example B"l 17).
melting point 290°C
NMIl (DMSO-d(s)S: 2.08(3H, s), 3.44-4.2l(5H, m), 4,5l(2H, d, 5.7Hz), 4.93(lH, m), 5.46-5.62(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.49(lH, s), 10.40(1H, t, 5.7Hz), 11.48(1H, s).
An Example compound H-2 was synthesized according to the same manner as that of Example H-l.
Example H"2)
l-Acetyl-5-hydroxy6,10'dioxo-l,2,3,4,6,9,9a,10"octahydro-l,4a,8a-triaza-anthracene-7 •carboxylic acid 4-fluorobenzylamide
melting point: 290°C
NMR (DMSO-de)8: 1.95(2H, m), 2.14(3H, s), 2.85(2H, m), 4.45(4H, m), 4.5l(2H, d, 5.7Hz). 5.99(1H, s), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.37(lH. s), 10.46(lH, s), 12.28(1H, s).
Example l-l)
109
5"Hydroxy-l-methanesulfonjd-4,6-dioxo-2,3,4,6,9,9a-hexahydro-lH"l,3a,8a-triaza-cycl open ta[b] naphthalene-7-carboxylic acid 4-fluorobenzylamide
[Chemical formula 62]

l) To a solution of a compound 48,(140 mg, 0.30 mmol) in pyridine (1.4 ml) were added methanesulfonyl chloride (28 pi, 0.36 mmol), and 4dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 3 hours. After 2N hydrochloric acid was added, this was extracted with ethyl acetate, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure. Diisopropylether was added to crystallize the material, which was filtered to obtain 54 (127 mg) as a pale orange crystal at a yield of 78 %.
2) According to the method of Example Bl 17), an Example compound 1-1 (21 mg) was obtained at a yield of 21 % from a compound 54 (123 mg).
melting point: 260°C
NMR (DMSO-dG)8: 3.16(3H, s), 3.30-4,15(5H, m), 4.45(2H, d, 5.7Hz), 4.27(2H, m), 5.36(1H, m), 7.14(2H, t, 8.7Hz), 7.33(2H, m), 8.22(lH, s), 10.53(lH, s).
According to the same manner as that of Example J-l, an Example compound l"2 was synthesized.
Example 1-2)
5-Hydroxy-l"methanesulfonyl-6,10-dioxo-l,2,3,4,6,9,9a,10-octahydro-l,4a,8a-triazaan thracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 257-259°C
NMR (DMSO-de)5: 1.80-1.96(2H. m), 3.02-3.58(2H, m), 3.16(3H, s), 4.76(2H, m), 5.56(111, s), 7.16(2H, t, 9.0Hz), 7.35(2H, m), 8.36(lH, s), 10.39(lH, s).
Example L'l)
110
5,9-Dihydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro'lH-2-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro"benzylamide
(Chemical formula 65]

1) According to the method of synthesizing- a compound 66, a compound 62 (278 rag, 57%) was obtained from a compound 13 (357 mg).
2) According- to the method of synthesizing a compound 57, a compound 63 (202 mg, 79 %) was obtained from a compound 62 (278 mg).
3) To a solution of a compound 63 (200 mg, 0.403 mmol) in chloroform (2 ml) were added dimethyl sulfoxide (286 fxl, 4.03 mmol), and triethylamine (337 |xl, 2.42 mmol), the mixture was stirred for 10 minutes under ice-cooling, a sulfur trioxide-pyridine complex (321 mg, 2.02 mmol) was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution was added water (3 ml), and chloroform was distilled off under reduced pressure, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The crystalline residue was washed with ethyl acetate to obtain a compound 64 (60 mg) at a yield of 30 %.
4) Using a compound 64, and according to the method of synthesizing Example A-l, an Example compound L"l was synthesized.

NMR (DMSO-dfi)6-' 2.98-3.10(1H, m), 3.38-3.60(2H, m), 3.80-4.20(5H, m), 4.404.55(2H, m), 5.48(1H, brs), 5.85(lH, s), 7.15(2H, t, J=8.4Hz), 7.33"7.37(2H, m), 8.45(1H, s), 8.60(1H, s), 10.27-10.42(1H, m), 12.610.H, brs).

Example M/l)
111
l-Hydroxy-2,10-dioxo-2,4b,5,6,7,8,9,10octahydro-4a,9a-diaza-benzq[a]azulene-3-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 66]

l) According to the method of synthesizing a compound 21, a compound 65 (207 mg) was obtained at a yield of 24 % from a compound 13 (250 mg).
2) According to the method of synthesizing a compound 64, a compound 66 (313 mg, 67 %) was obtained from a compound 65 (470 mg).
3) After trifluoroacetic acid (10 ml) was added to a compound 66 (100 mg, 0.020 mmol), the mixture was stirred at 75°C for 4 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water. This was washed with an aqueous saturated sodium bicarbonate solution, a 10 % aqueous citric acid solution, and water, and dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, and fractions eluted with chlorofornvmethanol were concentrated under reduced pressure, and recrystallized with ethyl acetatediisopropyl ether to obtain an Example compound Ml (23 mg, 16 %).
melting point 281-283°C
NMR (DMSO-d(j)8: 1.43-1.52(211, m), 1.62-1.83(3H, m), 2.04-2.18(lH, m), 2.23-2.35(lH, m), 4.08-4.16(111, m), 4,48-4,53(2H, m), 5.58-5.61(1H, m), 7.11-7.20(2H, m), 7.30-7.38(2H, m), 8.29(1H, s), 10.30-10.36(lH, m), 12.78(lH, brs).
Example X-l)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,ll,lla-hexahydro-lH-pyrido[l,2-a]pyrrolo[l,2-d]pyrazine-8-carboxylic acid 4-fluoro-benzyJ.amide
[Chemical formula 67]
112

l) Selenium dioxide (666mg, 6.0mmol) was added to the solution of compound 2 (216mg, l.Ommol) in bromobenzene (2ml). Then the mixture was heated up to 160°C, and stirred for 16h. After celite filtration the solvent was evaporate. The precipitate was purified by silicagel column chromatography, and fractions eluting with ivhexan/EtOAc were concentrated under reduced pressure to obtain compound 100 (l64mg, 71%) as a yellow oil.
1H-NMR (CDCUS: 5.52(1H, s), 6.50(1H, d, J=6.0Hz), 7.36(5H, m), 7.74(lH, d, J=6.3Hz), 9.88(1H, s).
2) Sulfamic acid (l.50g, 15.4mmol') and NaCl02 (l.05g, 11.6mmol) was added to the solution of compound 100 (2.54g, ll.Ommol) in acetone (20ml) and water (30ml). Then the mixture was stirred for 3h. The solvent was evaporated under reduced pressure to obtain compound 101 (2.18mg, 80%) as a white solid.
1H-NMR (DMSOde)S: 5.1l(2H, s), 6.55(lH, d, J=5.4Hz), 7.32-7.46(5H, m), 8.2l(lH, d, J=5.7Hz).
3) (R)-2-N-BOCaminomethyl pyrrolidine (391mg, 1.95mmol) was added to the solution of compound 101 (400mg, 1.62mmol),
113

l-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (373mg, 1.95mmol), and 1-hydroxybenzotriazole (219mg, 1.62mmol) in THF (6ml). After sttiring for 16h NaHCOa aqueous solution was added to the mixture. The mixture was extracted with EtOAc, which was washed with NH-iCl aqueous solution and brine. The organic phase was dried over MgSO.i, After a filtration the solvent was removed under reduced pressure to obtain compound 102 (694mg, 100%) as a white solid.
1H-NMR (CDC13)8: 1.46(9H. s), 1.56-2.14(4H, m), 3.29(4H, m), 4.18(lH, m), 5.24(1H, s), 6.27(1H, s), 6.46(1H. d, J=5.7Hz), 7.35(5H, m), 7.69(lH, d, J=5.7Hz).

4) The solution of compound 102 (694mg, ,1.95mmol) in HCl/EtOAc (4mol/l, 8ml) was stirred for 30 min. The soluvant was removed under reduced pressur, diluted with EtOH (16ml) then. A saturated NaHCOa aqueous solution was added to the solution to control pH at 9. The mixture was strred at 50 °C for 2h, then diluted with water. The mixture was extracted with CHCl3, washed with brine, and dried over MgSO-i. The solvent was removed under reduced pressure to obtain compound 103 (413mg, 68%) as a yellow solid.
1H-NMR (CDCla)8: 1.54-2.22(4H, m), 3.60(2H, m), 3.80UH, t, J=12.0Hz), 4.18(lH. d, J=12.0Hz), 5.15(1H, d, J=9.9Hz), 5.35(lH, d, J=9.9Hz), 6.7l(lH, d, J=5.4Hz), 7.33(3H, m), 7.50(1H, d, J=5.lHz), 7.63(2H, d, J=7.2Hz).
5) NaOAc (ll8mg, 1.44mmol) and bromine (0.234ml, 2.62mmol) were added to the solution of compound 103 (408mg, 1.31mmol) in acetic acid (8ml), stirred for 30 min then. An aqueous solution of NaOH (2M) was added to the mixture, and extracted with CH2Cl2, washed with brine, and dried over NaSO-i. The solvent was removed under reduced pressure to give compound 104 (390mg, 77%) as a white solid.
1H-NME. (CDC13)8: 1.56-2.19(4H, m), 3.55-4.02(5H, in), 5.12(111, d, J=9.6Hz), 5.35(lH, d, J=9.9Hz)J 7.29-7.38(3H, m), 7.6l(lH, s), 7.67(2H, d, J=6.6Hz).
6) Tetrakis triphenylphosphine paradium (0) (77mg, 0.067mmol) and N.N'diisopropylethylamine (0.29ml, 1.67mmol) were added to the solution of compound 104 (l30mg, 0,334mmol) in DMSO (2.6ml). the mixture was stirred under CO atmosphere for 2h at 80°C . The reaction mixture was diluted with a saturated NrLiCl aqueous solution, extracted with EtOAc then. And the organic phase was washed with brine, and dried over NasSO-i. The precipitate was purified by silicagel column chromatography, and fractions eluting with MeOH/EtOAc were concentrated
114

under reduced pressure to obtain compound 105 (II5mg, 75%) as a white oil.
1H-NMR (CDCIs)6: 1.56-2.33(4H, m), 3.66(211, m), 3.90(2H, m), 4,19(IH. s), 4.66(2H, m), 5.20(.1H, d, J=9.9Hz), 5.37(IH, d, J=9.9Hz), 7.00(2H, t, J=8.7Hz), 7.33(5H, m), 7.6K2H, m), 8.39(1H, m), 10.50(1H, s).
7) A mixture of compound 105 (IIImg, 0.241mmol) and paradiumcarbon (10%, 22mg) in THF (8ml) and MeOH (2ml) was stirred under hydrogen atmosphere for 3h. After celite filterat.ion the solvent was removed under reduced pressure to give the example X-I (57mg, 64%) as a white solid.
Melting point: 274°C
1H-NMR (DMSO-dG)8:1.56-2.25(41-1, m), 3.48-3.65(2H, in), 4.0I(2H, m), 4.5I(2H, d, J=5.7Hz), 4,71(1H, d, J=9.9Hz), 7.14(2H, t, J=9.0Hz), 7.33(2H, dd, J=5.7, 8.7Hz), 8.4I(IH, s), 10.44(.IH, t, J=6.0Hz), 12.18(IH, s).
The following compounds were synthesized using the similar method.
Example X-2)
{R)-6-Hydroxy-5,7-dioxo-2,3,5,7,II,IIa-hexahydro-IH-pyrido[I,2- ine-8-carboxylic acid 2,4-difluoro-benzylamide
Melting point: 300°C
IH-NMR'(DMSO-do)6: 1.03-2.20(4H, m), 3.39-3.66C2H, m), 4.02(2H, m), 4,54(2H, d, J=6.0Hz), 4.71(1H, d, J=9.9Hz), 7.06(IH, m), 7.23(IH, m), 7.38(IH, m), 8.4I(IH. s), 10.43(1H, t, J=6.0Hz), 12.19(1H, s).
Example X-3)
(R)-6-.Hydroxy5,7-dioxo-2,3,5,7,II,IIa'hexahydro-IH-pyndo[I,2-a]pyrrolo[I,2-dJpyraz ine-8-carboxylic acid 3chloro-2-fruoro-benzylamide
Melting point: 304°C
1H-NMR (DMSO-d6)8: 3.44-3.66(2H, m), 4.0K2H, m), 4.61(2H, d, J=5.4Hz), 4.70(IH, d, J=9.0Hz). 7.20(1H, in). 7.3I(IH, m), 7.49(IH, m), 8.4KIH, s), 10.49(IH, t, J=5.7Hz), 12.20(1H, s).
Example X'4)
I-Hydroxy-2,9-dioxo-2,5,6,7,8,9,10,10aoctahydro-4a,8a-diaza-anthracene-3-carboxylic acid 4-fluoro'benzylamide
115

Melting point: 259°C
1H-NMR 14.1Hz), 4.38(1H, d, J=12.9Hz), 4.53(3H, m), 7.16(2H, t, J=9.0Hz), 7.34(2H, dd, J=5.7, 8.7Hz), 8,39(1H, s), 10.44(1H, t, J=6.3Hz), 12.84UH, s).
According to the same manner as that of Example C'21, the following Example compounds Y-I to Y-18 were synthesized.
Example Y-I)
(3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,I0-hexahydro-2H-I-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y9)
(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a, IO-hexahydro-2H"I-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (CDC13)S: 0.90(3H, d, J=6.9Hz), 2.00-2.10(IH, m), 2.70(IH, dd, J=11.6, 13.4Hz), 3.41(1H, dd, J=11.2, 12.9Hz), 4,05-4.45(2H, m), 4,30-4,38(IH, dd, J=4,0, 14.1Hz), 4.63(2H, d, J=5.9Hz), 4.65-4.75(IH, m), 4,98(.1H, t, J=3.7Hz), 6.80-6.84(2H, m), 7.32-7.40(111, m), 8.3I(IH, s), 10.38(IH, brs), 12.37(IH, s).
Example Y-2)
(4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-I-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y3)
(4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-I-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (CDC13)6: 1.42(3H, d, J=7.0Hz), 1.56(IH, dd, J=2.0, 14.0Hz), 2.19-2.30(].H, in), 4.02(1H, d, J=2.2liz), 4.05(IH, t, J=2.3Hz), 4.12(IH, dd, J=6.0, 13.6Hz), 4.27(1H, dd, J=4.2, 13.4Hz), 4,64(2H, d, J=5.9Hz), 4.95-5.05(IH, m), 5.26(2H, d, J=4,I, 5.8Hz), 6.75-6.85(2H, m), 7.30-7.40OH, m), 8.30(1H, s), I0.38(1H, brs), 12.45(1H, s).
Example Y"4)
(2R19aR)-5-Hydroxy-2-metlioxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-.I-oxa-4 a,8a-diaza-anthracene-7carboxylic acid 2,4-difluoro-benzylamide
Example Y8)
(2S,9aS)-5-Hydi'0xy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-.I-oxa-4a
116

,8a-diaza-anthracene-7 xarboxylic acid 2,4-difluoro-benzylamide
1H-NMR (CDCIs)6: 1.60-1.80(2H, m), 3.09-3.2I(IH, m), 3.37(3H, s), 3.35-3.50(2H, m), 4.00-4.1K1.H, m). 4.24UH. d, J=13.1Hz), 4.36(IH, d, J=10.IHz), 4.64(1H, d, J=5.9Hz), 4.70-4.80(IH, m), 5.12(1H, s), 6.75-6.85(2H, m), 7.30-7.40(IH, m), 8.30(IH, s), 10.380.H, brs), 12.33(IH, brs).
Example Y-5)
(5aR,6aS,10aR)- I-Hydroxy-2,12-dioxo-2,5,5a,7,8,9,10,10a, 11,12-decahydro-6aH-6-oxa-4a,IIa-diaza-naphthacene-3-carboxylic acid 2,4-difluoro-benzylamide [racemate]
1H-NMR (DMSO-d6)8: 1.00-1.85(911, m), 2.90(IH, t, J=4.2Hz), 4.36(.1H, dd, J=4.2, 12.9Hz), 4.44-4,57(4H, m), 5.32(IH, t, J=3.9Hz), 7.03-7.09(IH, m), 7.20-7.27(IH, in), 7.35-7.43(1H, m), 8.49(I.H, s), 10.34(1H, brs).
Example Y"6)
(2S,9aR)-2Ethyl-5hydroxy-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-I-oxa-4a,8a-diaza-anthracene'7-carboxylic acid 2,4-difluoro-benzylamide
Example Y7)
(2R,9aS)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-I-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)8: 0.87(3H, d, J=5.4Hz), 1.40-1.5I(3H, m), 1.75(IH, d, J=10.8Hz), 3.22(1H, t, J=10.2Hz), 3.73-3.78(IH, in), 4.41-4.57(4H, m), 5.29(IH, s), 7.03-7.07(IH, in), 7.21-7.26Q.H, m), 7.37-7.42(IH, m), 8.50(1H, s), 10.34(IH, brs), 12.48(IH, s).
Example Y-10)
(2S,9aS)-5-Hydroxy-6,10-dioxo-2-phenyl-3,4,6,9,9a, 10-hexahydro-2H-I-oxa-4a,8a-diaz

aanthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (CDC13)8: 1.701.82(IH, m), 1.98(IH, d, J=9.6Hz), 3.49(1H. t, J=9.6Hz), 4.54-4.68(6H, m), 4.98(IH, d, J=8.7Hz), 5.5I(IH, s), 7.04-7.08(IH, m), 7.21-7.42(7H, m), 8.50(111, s), 10.38(1H, s), 12.45(1H, s).
Example Y-II)
(2S,9aS)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7carboxylic acid 2,4-difluoro-benzylamide
Example Y12)
(2R,9aR)-5-Hydroxy-2-isopiopyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-l-oxa-4a,8a-di
117

aza-anthracene-7'carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)8: 0.86(6H, dd, J=4.8, 13.5Hz), 1.4M.49(1H, m), 1.57-1.69(1H, m), 1.72-1.78(1H, m), 3.20(IH, t, J=8.4Hz), 3.52-3.59(IH, m), 4.41-4.46(5H, m), 5.29(1H, s), 7.01-7.08(1H, m), 7.21-7.26(IH, m), 7.37-7.43(IH, m), 8.50(IH, s), 10.35(1H, brs), 12.48(111, s).
Example Y-13)
(3S,9aS)-5-Hydroxy-3-raethy]-6110-dioxo-3,4,6)9,9a,10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-earboxylic acid 4-fluoro-benzylamide
Example Y-14)
(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
1H-NMR (DMSO-d6)8: 0.8l(3H,d, J=6.6Hz), 1.84-1.93(1H, m), 2.86(1H, t, J=12.5Hz), 3.48(1H, t, JXI.l.IHz), 3.97-4.03(.IH, m), 4,41-4.60(3H, m), 4,52(2H, d, J=5.9Hz), 5.20(1H, t, J=3.8Hz), 7.12-7.20(2H, m), 7.32-7.38(2H, m), 8.52(IH, s), 10.36(IH, fc, J=5.9Hz), 12.45(1H, s).
Example Y-15)
(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-16)
(2S)9aR)-5-Hydroxy-2-methyl-6J10-dioxo-314,6,9,9a,10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4'di.fluoro-benzylamide
1H-NMR (DMSO-d6)S: 1.14(3H, d, J=6.0Hz), 1.38(1H, m). 1.75(IH, d, J=13.8Hz), 3.18-3.29(1H, m), 3.95-4.06(IH. m), 4.42-4.58(311, in), 4,54(2H, d, J=5.7Hz), 5.30(1H, t, J=3.9Hz), 7.03-7.10(1H, m), 7.20-7.29(IH, m), 7.35-7.44(IH, m), 8.50(IH, s), 10.35UH, t, J=5.7Hz), 12.48(1H, s).
Example Y17)
(2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a-diaza-aathracene-7-carboxylic acid 4-fluonrbenzylamidc
Example Y18)
(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
1H-NMR (DMSO-d6)S: 1.15(3H, d, J=6,0Hz), 1.35-1.50(IH, m), 1.75(IH, d, J=12.9Hz),
118

3.23(1H, td, J=13.0, 2.8Hz), 3.96-4.03(IH, m),4.41-4.59(3H, m), 4.52(2H, d, J=6.0Hz), 5.30(1H, t, J=3.9Hz), 7.12-7.19(2H, in), 7.32-7.38(211, m), 8.52(IH, s), 10.36(1H, t, J=6.0H.z), 12.48(1H, s).
Corresponding amino-alcohol derivatives used in syntheses of Y-l to Y-.18 were prepared as optically pure version using methods similar to those described in the following reports.
3-Amiiio-2-methyl-propan-l-ol, and 4-Ammo-butan"2-ol were prepared according to the method of Russell A. Barrow (J.Am. Chem. Soc. 1995, 117, 2479-2490).
3-Amino-butan-l-ol were prepared according to the method of P. Besse (Tetrahedron Asymmetry 10(1999) 2213-2224).
l-Amino-pentan-3-ol, l'Amino-4-methyl-pentarr3"ol, 4-Amino-l-methoxy-butan-2-ol, and 3-Amino*l-phenyl-propan-l-ol were prepared according to the method described in the following literatures, U.S. Pat. Appl. Publ., 2004133029, 08 Jul 2004, PCT Int. Appl., 2002012173, 14 Feb 2002.
All examples below consist of >95% ee and >6'1 diastereomeric purity unless indicated otherwise. The compounds shown in table ZZ consist of mixtures of diastereomers at the depicted stereocenter in ratios of 1U. to >10:.I. Stereocenters that were formed during the process' below have been assigned using NMR techniques well know in the art (ID and 2D method) and/or using vibrational circular dichroism techniques. Stereochemical assignment determinatons were performed on representative examples and closely related compounds were assigned by analogy in some cases. The schemes below are meant to be general guidance to how examples were synthesized. It will be possible that one skilled in the art may rearrange the order of steps or change substituents to apply the method described below and in the examples to construct compounds of the general formula. Additional methods known to those skilled in the art or commonly present in the literature may also be applied
119

to perform similar transformations and arriving at the same compounds of the general formula or amino alcohol and diamine precursors.
120
[Chemical formula 68]

121

122

123

124

125

126

127

Example Z-I-
(3 ft. I.Ia6)-A-[(2,4-Difluorophenyl)methvl]-6-hvdroxv-3-methvi-5,7-dioxo-2,3,5.7,II.IIa
-hexahydrofl,3loxazolof3,2',dpvridofl.2-flf]pvrazmc-8-carboxarnide sodium salt.

(3/?,IIa6)-A':[(2,4-Difluorophenyl)meth.vl]-3-iTiethyl-5,7-dioxo-6-t(phenylmethyl)oxy]-2,
3,5,7,11, IIa-hexahydro[I, 3] oxazolof.3,2-a]pyrido[I,2-fl'Ipyrazine-8-cai'boxamide. To a
solution of 16a (409 mg, 0.87 mmol) in dichloroethane (20 mL) was added
128

(2_/?)-2-amino- 1-propanol (0,14 mL, 1.74 minol) and 10 drops of glacial acetic acid.
The resultant solution was heated at reflux for 2 h. Upon cooling, Celite was added
to the mixture and the solvents removed in vacuo and the material was purified via
silica gel chromatography (2% CH3OH/CH2Cl2 gradient elution) to give
(3A>,IIa6)A':I(2,4-difluorophenyl)methyl3-3-methyl-5,7-dioxo-6-f(phenylmethyl)oxy]-2,
3,5,7,II,IIa-hexahydro[I,3]oxazolo[3,2-,dpyrido[I,2-c/]pyrazine-8-carboxamide (396
rag, 92%) as a glass. 'H NMR (CDCIs) 8 10.38 (m, 1 H), 8.42 (s, 1 H), 7.54>7.53 (m, 2
H), 7.37-7.24 (m, 4 H), 6.83-6.76 (m, 2 H), 5.40 (d, J= 10.0 Hz, 1 H), 5.22 (d, J= 10.0
Hz, 1 H), 5.16 (dd, J= 9.6, 6.0 Hz, 1 H), 4,62 (m, 2 H), 4,41 (m, 1 H), 4.33-4.30 (m, 2
H), 3.84 (dd, J= 12.0, 10.0 Hz, 1 H), 3.63 (dd, J- 8.4, 7.2 Hz, 1 H), 1.37 (d, J= 6.0 Hz,
3 H); ES+ MS: 496 (M+I).
b)
(3/ -hexahydi,o[.I,3]oxazolo[3,2-a]pyriclo[I,2-fl']pyrazine-8-carboxainide sodium salt. To a
solution of
(37?,IIa)-A[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxyJ-2,
3,5,7,II,IIa-hexahydro[I,3]oxazalo[3,2v?Jp3aido[I,2<3']pyrazine-8-carboxamide (396
mg-, 0.80 mmol) in methanol (30 mL) was added 10% Pd/C (25 mg). Hydrogen was
bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture
was filtered through Celite with methanol and dichloromethane. The filtrate was
concentrated in vacuo to give
(3/2,IIa-A[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,II,IIa-
129

hexahydro[I,3]oxazolo(3,2-a]pyrido[I,2-*/]pyrazine-8-carboxamide as a pink tinted
white solid (278 mg, 86%). 'H NMR (CDCIs) 6 11.47 (m, 1 H), 10.29 (m, 1 H), 8.32 (s,
1 H), 7.36 (m, 1 H), 6.82 (m, 2 H), 5.31 (dd, J= 9.6, 3.6 Hz, 1 H), 4.65 (m, 2 H),
4.47-4.38 (m, 3 H), 3.93 (dd, J~ 12.0, 10.0 Hz, 1 H), 3.75 (m, 1 H), 1.49 (d, J= 5.6 Hz,
3 H); ES+ MS-- 406 (M+I). The above material (278 mg, 0.66 mmol) was taken up
in ethanol (10 raL) and treated with 1 ./V sodium hydroxide (aq) (0.66 mL, 0.66 mmol).
The resulting suspension was stirred at room temperature for 30 min. Ether was
added and the liquids were collected to provide the sodium salt of the title compound
as a white powder (291 mg, 99%).* >H NMR (DMSOflVi) o 10.68 (m, 1 H), 7.90 (s, 1 H),
7.35 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.20 (m, 1 H), 4,58 (m, 1 H), 4,49 (m, 2 H),
4.22 (m, 2 H), 3.74 (dd, J= 11.2, 10.4 Hz, 1 H), 3.58 (m, 1 H), 1.25 (cl, J= 4,4 Hz, 3 H).
Example Z-2:
(4ai?.13a6)-A-K2,4-DifluoroTJhenvl)methvl]-10-hvdroxv-9.11.-dioxo-2.3.4a.5.9.11,13.13a
-octahvdro'l/f-pvridofl.2-a]pvrrolo[r.2':3.4-]imidazoll.2-c/]pyrazine-8-carboxamide.

(4a/?,13a6)-jV-[(2,4-Diiluorophenyl)methyl]-9,II-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5
,9,II,13,.13a-octahydrolN'-pyrido[I,2-,7]pyrrolo[I',2"3,4]imidazo[II2-rflpyrazine-8-carb
oxamide. A solution of 16a (24 mg, 0.05 mmol), [(2i5)-2-pyrrolidinylmethyl]amine (0.1
mL) and 2 drops of glacial acetic acid were heated under microwave conditions at 140
130

°C for 10 min. Upon cooling, Celite was added to the mixture and the solvents
removed in vacuo and the material was purified via silica gel chromatography (2%
CH3OH/CH2Cl2 gradient elution) to give
(4ai?,13a5)-A[(2,4-difluorophenyl)methyl]-91].I-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,
9,11, IS.ISa-octahydro-liir-pyridofl-aJpyrrololI'.Z'Slimidazotl-rflpyrazine-S-carbo
xamide (19 mg, 71%) as a white solid. 'H NMR (CDC1.0 8 10.41 (m, 1 H), 8.38 (s, I
H), 7.56 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.38 (d, J= 9.6 Hz, 1 H), 5.10 (d, J
= 10.0 Hz, 1 H), 4,62 (m, 2 H), 4,40 (m, 1 H), 4.25 (dd, J= 12.0, 6.8 Hz, 1 H), 4.10 (d, J
= 12.8 Hz, 1 H), 3.83 (m, 1 H), 3.71 (m, 1 H), 3.14-3.04 (m, 2 H), 2.78 (m, 1 H),
2.11-1.58 (m, 4 H); ES+ MS'- 521 (M+I).
b)
(4a7?,13a6)-iV-[(2,4-Difluoropheny])methyl]-10-hydroxy-9,II-dioxo-2,3,4a,5,9,III13,13a
-octahydro-I./-pyrido[I,2-]pyrrolo[r,2':3,4]imidazo[I,2-fl']pyrazine-8-carboxamide.
To a solution of
(4a/i,13a6)-Ar-[(2,4-difluorophenyl)methyl]-9,II-dioxo-10-[(phenylmethy])oxy]-2,3,4a,5,
OISSa-octahydro-liZ-pyridoCl-aJpyrrolofr'iimidazofl-rflpyrazine-S-carbo

xamide (19 mg, 0.04 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture was filtered through Celite with methanol and dichloromethane.

The filtrate was concentrated in- vacuo to give the title compound (6 mg, 38%) as a white solid. >H NMR (CDCla) 5 11.73 (m, 1 H), 10.36 (m, J. H), 8.31 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 4,62 (m, 2 H), 4,50 (m, 1 H), 4,27-4.19 (m, 2 H), 3.87-3.77 (m, 2 H),
131

3.16-3.08 (m, 2 H), 2.83 (m, 1 H),"2.11-1.65 (m, 4 H); ES* MS: 431 (M+l).
Example Z'3-'
(3a6,.13a6)-A[(2.4-DifluorODheiivl)methvl|-8-hvdroxv-7.9-dioxo-1.2.3.3a.4.5.7.9.13.13a -decahvdropvridofl\2':4,5]pvra7inoll,2-a]pvrrolo(l.2-dpvrimidine-10-carboxamide.

a) ABOC-(2 (4.17 g, 19.4 mmol) in THF (40 mL) at 0 "C was added BH3-THF (21.4 mL, 1 M in THE, 21.4 mmol) drop wise. The bath was removed and the resultant solution stirred at room temperature for 2 h. Methanol was added to quench the mixture and the solvents were removed N; vacuo. The residue was taken up in ethyl acetate and washed with sodium bicarbonate and brine. The aqueous layers were extracted twice with ethyl acetate. The combined organics were dried over NasSOi, filtered and concentrated to give 7V-BOO(2.S)-2-(hydroxymethyl)-l-py)Tolidine (3.82 g, 98%) as a clear oil. This material was used without further purification. 'H NMR (CDChi) 5 3.94 (m, 1 H), 3.62 (dd, J= 11.2, 3.2 Hz, 1 H), 3.56 (dd, J= 10.8, 7.2 Hz, 1 H), 3.44 (m, l H), 3.29 (m, 1. H), 2.62 (br, 1 H)r1.98 (m, 1 H), 1.85-1.72 (m, 2 H), 1.58 (m, 1 H).
b) N-BOC-(26)-2-({[(4-Methylphenyl)sulfonyl]oxy>methyl)-l-pyrrolidine. To a cold (0 °C) solution of A-BOC-(26)-2-(hydroxymethyl)-lpyrrolidine (350 mg, 1.74 mmol) in dichloromethane (20 mL) was added triethylamine (0.29 mL, 2.08 mmol), and
132

toluenesulfonyl chloride (398 rag, 2.08 mmol). AjVdemethylaminopyridine (70 mg) was added and the resultant solution was allowed to warm to rt as the bath warmed and stirred for 4 h. Water was added and the layers separated. The aqueous layer was washed with sodium bicarbonate and then with brine. The combined organics were dried over Na2SO-i, filtered and concentrated followed by flash chromatography purification to give -
AcBOC-(2S)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-l-pyrrolidine (460 mg, 75%) as a clear oil. 'H NMR exists as rotomers (CDCla) o 7.77 (d, 2 li), 7.33 (m, 2 H), 4.08 (m, .1 H), 3.97-3.88 (m, 1 H), 3.353.25 (m, 2 H), 2.43 (s, 3 H), 1.95-1.79 (m, 4 H), 1.40 and 1.35 (s, 9 H rotomeric BOC -butyl).
c) 7V-BOC-(26)-2-Cyano-l-pyrrolidine. A mixture of-
Ar-BOC-(25)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-l-pyrrolidine (460 mg, 1.29 mmol) and KCN (256 mg, 3.88 mmol) were heated at 90 "C in DMSO (10 mL) for 6.5 h. The mixture was cooled to room temperature and KtOAc and water were added. The organics were washed with water twice and then with brine. The aqueous layers were extracted with EtOAc and the combined organics dried over NaaSO-j, filtered and concentrated followed by flash chromatography purification to give Af-BOO (2£)-2cyano-pyrrolidine (179 mg, 66%) as an oil. 'PI NMR exists as rotomers (CDCla) 6 3.99 (m, 1 H), 3.43-3.37 (m, 2 H), 2.83-2.51 (m, 2 H), 2.17-1.83 (m, 4 H), 1.46 and 1.44 (s, 9 H rotomeric BOC butyl).
d) Af-BOC-(2£)-2-(2-Aminoethyl)-l-pyrrolidine. A solution of MBOC-
133

(26)-2-cyancr pyrrolidine (179 mg, 0.85 ramol) in ethanol saturated with anhydrous ammonia was treated with RaneyNi (l mL of 50% aq. Suspension) and 50 psi of H2 overnight. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (10% CH3OH/CH2CI2 with 1% NH-iOH gradient elution) through a short plug of silica gel to give -
A-BOC-(2£)-2-(2-aminoethyl)-l-pyrrolidine (90 mg, 50%) as a clear oil. 'H NMR exists as rotomers (CDCla) 6 3.88-3.77 (m, 1 ID, 3.33-3.24 (m, 2 H;, 2.66 (m, 2 H), 1.89-1.54 (m, 6 H), 1.40 (s, 9 H).
e) {2((26)-2-Pyrrolidinyl]ethyl}amine. A solution of-

A-BOC(2£)-2-(2-aminoethyl)-l-pyrrolidine (90 mg, 0.42 mmol) in THF (6 mL) was treated with 4 N HC1 (aq) (2 mL) and stirred at room temperature for 3 h. The mixture was concentrated in vacuo to give the title compound as its HC1 salt. A portion of this material (40 mg) was dissolved in methanol and treated with solid supported carbonate resin (MI'-Carbonate, Argonaut Technologies) to freebase the amines. After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully in vacuo to give {2-[(25)-2-pyrrolidinyl]ethyl}amine (30 mg) as its free base. >H NMR (CDCla) o 3.06 (m, 1 H), 2.94 (m, 1 H), 2.83 (m, 1 H), 2.79-2.69 (m, 2 H), 1.90-1.56 (m, 6 H).
f)
(3a5,,13a6)-A'-[(2,4-Difluorophenyl)methyl)-7,9-dioxo-8-[(pheiiylmethyl)oxy]-l,2,3,3a,4, 5,7,9,13,13a-decahydropyridolr,2'-'4,5]pyrazino[l,2-j7]pyrrolo(l,2-c]pyrimidine-10-carb
134

oxamide. A solution of 16a (30 mg, 0.06 mmol), {2-[(2£)-2-pyi-rolidinyl]ethyl}amine (30 mg, 0.26mmol) and 2 drops of glacial acetic acid were heated under microwave conditions at 140 °C for 10 min. Upon cooling, Celite was added to the mixture and the solvents removed in vacuo and the material was purified via silica gel chromatography (2% CH3OH/CH2CI2 gradient elution) to give
(3aiS,113a-N-K214-Difluorophenyl)inethyl]-7,9-dioxo-S-[(phenylmethyl)oxy]-l,2,3,3a,4, 5,7,9,13,13a-decahydropyridoll',24,5]pyrazinol 1,2-Jpyrrolo[l,2-dpyrimidine-10-carb oxamide. (25 mg, 74%) as a film. »H NMR (CDCla) 6 10.44 (m, 1 H), 8.32 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.28-5.22 (m, 2 H), 4.67 (dd, 2.8 Hz, 1 H), 4.62 (m, 2 H), 4.26 (m, 1 H), 4.11-4.03 (m, 2 H), 2.91 (m, 1 H), 2.81 (m,
1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.92 (m, 1 H), 1.82-1.76 (m, 3 H), 1.52-1.38 (m, 2 H);

ES'MS: 535 (M+l).
g)
(3a-.9,13a5)-7V-[(2(4-Difluorophenyl)meth.ylj-8-hydroxy-719-dioxo-l,2,313a,4,5)7,9,13,13a
-clecahydropyrido[r,2'-4,5]pyrazinoll,2-a]pyrrolo[l,2-dpyi'iinidine-10-carboxamide.
To a solution of
(3a5,,l3a6)-Ar-[(2,4-difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-l,2,3,3a,4>
5,7,9,13,13a-decahydropyrido[r,2':4,5.]pyrazino[l,2-]pyrrolo[l,2-dpyrimidine-10-carb
oxamide (25 mg, 0.05 mmol) in methanol (8 niL) was added 10% Pd/C (10 mg).
Hydrogen was bubbled through the reaction mixture via a balloon for 18 h. The
resultant mixture was filtered through Celite with methanol and dichloromethane.
The filtrate was concentrated in vacuo to give the title compound (14 mg, 67%) as a
135

white solid. 'H NMR (CDCl3) 0 12.53 (br, 1 H), 10.44 (s, 1 H), 8.29 (s, 1 H), 7.34 (m,
1 H), 6.78 (m, 2 H), 4.71-4,58 (m, 3 H), 4.29-4.14 (m, 3 H), 2.99 (in, 1 H), 2.88 (m, I H),
2.44 (m, 1 H), 2.30 (m, 1 H), 1.97-1.38 (m, 6 H); ES+ MS: 445 (M+l).
Example Z~4:
(4a>5'.13aig)-Ar-f(2.4-DijQuoroDhenvl)methvn-10-hvdroxv-9.11-dioxo-2,3.4a.5.9.11.13.13a
-octahydro-l/Z-pyrido[l,2-a]pyrrolo[l'.2':3,4]imidazol 1.2'o1pyrazine-8-carboxamide
sodium salt.

a) [(2i?)-2-PyrrolidinylmethylJamine. To a solution of
Af-BOC-(2/?)-2-(aminomethyl)-l-pyrrolidine (1.37 g, 6.85 mmol) in THF (20 mL) was
added 4 JVHCl (aq) (8 mL). The resultant solution was stirred at room temperature
overnight. The solvents were removed in vacuo and the residue was treated with
MP-carbonate resin in methanol and dichloromethane. After 1 h, the resin was
removed via filtration through a fritted tube and the volatiles were removed carefully
in vacuo to produce the free based amine (760 mg crude >100%) as a oil. This
material was used without further purification. 'H NMR (CDCl.j) 5 3.13 (m, 1 H),
2.92 (m, 1 H), 2.82-2.62 (m, 5 H), 1.88-1.30 (m, 4 H).
b)
(4a6",13ai£')-A':[(2,4-Difluorophenyl)methyl]-9,ll-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5
136

,9tll,l3,13a-octahydro-l/7-pyridofl,2-a]pyrrolo[l,,2,:3,4]imidazo{l,2-a']pyrazine-8-cai-b
oxamide. In a similar manner as described in example Z~2 from 16a (435 mg, 0.93
mmol) and [(279'2-pyrrolidinylmethyllamine (200 mg, 2.0 mmol) in
1,2-dichloroefchane (20 mL) and 15 drops of glacial acetic acid was obtained
(a-S'JSa/d-Ate-difluorophenyDmethyll-g.ll-dioxo-lO-KphenylmethyOoxyJ.Sa.S,
9,l.l,13,.13a-octahydro-l/cr-pyrido[l,2-a]pyrrolo[r,2'-'3,4]imidazo[l,2-a'lpyrazine-8-cai-bo
xamide (321 mg, 67%) as a white solid. »H NMR (CDCb) 6 10.41 (m, 1 H), 8.35 (s, 1
H), 7.56 (m, 2 H), 7.55-7.24 (m, 4 H), 6.80 (m, 2 H), 5.35 (d, J- 10.0 Hz, 1 H), 5.13 (d,
J= 10.0 Hz, 1 H), 4.60 (m, 2 H), 4.38 (dd, J= 10.4, 3.2 Hz, 1 H), 4,21 (dd, J= 12.0, 6.8
Hz, 1 H), 4,04 (dd, J- 12,4, 2.8 Hz, 1 H), 3.77 (apparent t, /= 11.6 Hz, 1 H), 3.68 (m,
1 H), 3.11-3.00 (m, 2 H), 2.75 (m, 1 H), 2.08-1.84 (in. 3 H), 1.65 (m, 1 H); ES' MS: 521
(M+l).
c)
(4a5',13a)-A-t(2,4-Difluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4a,5,9,ll,13,13a
-octahydro lNpyrido[l,2 •3]pyrroio[.l',2'-"3)43imidazo[l,2-a']pyrazine-8-carboxamide.
In a similar manner as described in example Z"2 from
(4a5',13a)-AA-K2,4-difluorophenyl)methyl3-9,.U-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,
9,ll,13,13a-octahydro-li/-pyrido[l,2-a]pyrrolo[l',2'-3,4]imidazo[l,2-rflpyrazine-8-carbo
xamide (518 mg, 0.99 mmol) and~10% Pd/C (35 mg) in methanol (40 mL) was obtained
(4a£,,13a/t')-A((2,4-Difluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4a,5,9,ll,13,13a
•octahydro-l-pyridotl-alpyrrololl'limidazoll-pyrazine-S-cai'boxamide
(430 mg, 99%) as a white solid. 'H NMR (CDCl3) 0 11.73 (m, 1 H), 10.36 (m, 1 H),
137

8.32 (s, 1 H), 7.35 (m, 1 H), 6.79 (m, 2 H), 4.64 (m, 2 H), 4.54 (dd, J = 10.8, 4.0 Hz, 1
H), 4.28-4.19 (m, 2 H), 3.90-3.79 (m, 2 H), 3.18-3.10 (m, 2 H), 2.84 (m, 1 H), 2.14-1.92
(m, 3 H), 1.72 (m. 1 H).
d)
(4a6',13a/i)-iV-[(2)4-Difluorophenyl)methyl3-10-hydroxy-9,ll-dioxo-213,4a,5,9,ll,13>13a
-octahydro-l-pyridofl-aJpyrrolotr.E'SJimidazofl-alpyrazine-S-cai-boxajnide
sodium salt. In a similar manner as described in example Z-l from
(4aS;i3a/e)-N-[(2,4-Difluorophenyl-)metliylJ-10-hydroxy-9,ll-dioxo-213,4a,5l9,ll,13,13a
-octahydro-li/-pyrido[.t,2-#]pyrrolo[l\2':3,4]imidazo[l,2-a']pyrazine-8-carboxamide
(430 mg, 1.0 mmol) and sodium hydroxide (l.O mL, 1.0 M aq, 1.0 mraol) in 20 raL of
ethanol was formed the corresponding sodium salt (425 mg, 94%) as a white solid.
'H NM.R (DaO) o 7.85 (s, 1 H), 7.23 (m, .1 H), 6.82 (m, 2 H), 4.51-4,46 (in, 3 H), 4.28 (m,
1 H),3.95 (in, 1 H), 3.84 (m, 1 H), 3.62 (m, 1 H), 3.16 (m, 1 H), 2.89 (m, 1 H), 2.84 (m,
1H), 1.90 (m, 2 H), 1.73 (m, 1 H), 1.60 (m, 1 H). ES+ MS: 431 (M+l).
Example 7,-5'
(4a6f. 13a7?)-Ar-[(4-Fluorop henyl)methvl]-10-hvdroxv-9.11-dioxo-2.3,4a.5,9.11,13,13a-oct
The title compound was made in two steps using a similar process to that described
138
ahvdro-3."-pvridofl.2-

in example Z-2. 16 (60 mg, 0.13 mmol) and l'(2/i?)-2-pyrrolidinylmethyl]amine (100
mg, 1.0 mmol) were reacted in dichloromethane (2 m.L) with acetic acid to give
(4a-S;i3a7d-A',-[(4-fluorophenyl)mefchyl]-9,ll-dioxo-10-[(phenylmethyl)oxy]--2,3t4a,5,9>l
1,13,13a-octahydro-lr"pyrido[l,2-a]pyrrolo[l'>2,-3,4jimidazo[l,2-ar]pyrazine-8-cai-boxa
mide (60 mg, 91%). This material was hydrogenated in a second step as described in
example Z-2 to give
(4al3a)-Ar-[(4-fluorophenyl)methyl]-10-hydroxy-9, ll-dioxo-2,3,4a,5,9,ll,13,13a-oct
ahydro-1 N-pyrido[l,2-5]pyrrolo[r,2' '3,4]imidazo[l,2'fl']pyrazine-8-carboxamide (21 mg,

anhydro-1 N-pyrido[l,2-3.]pyrrolo[l',2' 3,4:]imidazo[l,2 n]pyrazine-8-carboxamide (21 mg, 42%) as a white solid. >H NMR (CDCIs) 8 11.72 (m, 1 H), 1.37 (m, 1 H), 8.33 (s, 1 H), 7.29 (m, 2 H), 6.97 (m, 2 H), 4.57 (m, 2 H), 4.52 (m, 1 H), 4,24-4,19 (m, 2 H), 3.87-3.76 (m, 2 H), 3.14-3.07 (m, 2 H), 2.82 (m, 1 H), 2.11-1.89 (ra, 3 H), 1.68 (m, 1 H); ES+ MS: 413 (M+l).

Example Z-6:
(36',lla/£)-Ar-f(2,4-Difluorophenvl)methvll-6-hvdroxv-5.7-dioxo-3-(phenvlmethvl)-2.3,5.7,11. lla-hexahvdrofl.3]oxa2olo[3,2-fl]pvrido[l,2-flfJpyrazine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z'2. 16a (37 mg, 0.08 mmol) and (2 mg, 0.24 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(35,,].la/r!')-jV-f(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylinethyl)-6-[(phenylmethy
139

l)oxy]-2,3,5,7,ll)lla-hexahydro[l,3]oxazolo[3,2-]pyrido[l,2-fl']pyrazine-8-cai-boxamide (41 mg, 91%). This material was hydrogenafced in a second step as described in example Z'2 to give
(35;ilai(!)-A'-[{2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,ll,lla-hexahydiX)[l,3]oxazolo[3,2-a]pyrido[l,2-o1pyrazine-8-carboxamide. (25 mg, 75%) as a white solid. >H NMR (CDCIs) 5 11.47 (br, 1 H), 10.28 (in, 1 H), 8.35 (m, 1 H), 7.37-7.26 (m, 4 H), 7.18 (m, 2 H), 6.79 (m, 2 H), 5.03 (m, 1 H), 4.64-4.61 (m, 3 H), 4.40 (m, 1 H), 4.23 (apparent t, J= 7.2 Hz, 1 H), 3.96 (dd, J= 8.8, 6.4 Hz, 1 H), 3.88 (apparent t, J- 11.2 Hz, 1 H), 3.37 (dd, /= 13.6, 3.2 Hz, 1 H), 2.99 (dd, J= 13.2 8.8 Hz, 1 H); ES* MS: 482 (M+l).

Example Z-7-'
(3a6:i3a)-AA-K4-Fluoroi3henvl)methvl]-8-hvdroxv-7.9-dioxo-1.2.3.3a.4.5.7.9.13,13a-decahvdropyrido[l',2':4.5lpyrazino[1.2-a]pyrrolo[l.2-dpvrimidine-lQ-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16 (84 mg, 0.13 mmol) and {2-[(2,S)-2-.Pyrrolidmyl]ethyl} amine (150 mg, 1.3 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(3a6',13a6)-A':[(4-fluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxyJ-l,2,3,3a,4,5,7,9,13,13a-decahydropyrido[r,2':4,5]pyrazinoll,2a]pyrrolo[l,2-dpyrimidine-10-carboxamide (86 mg, 90%). This material was hydrogenated in a second step as described in
140

example Z-2 to give
(33.9,13a)-iV-r(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,33,4,5,7,9,13,13a-decahydropyrido[l\2':4,5]pyrazino[l,2-a]pyrrolo[l,2-dpyrimidine-10-carboxamide. (63 mg, 88%) as a white solid. 7.35 (m, 2 H), 6.94 (t, J= 8.8 Hz, 2 H), 4.63 (m, 1 H), 4.58-4.48 (m, 2 H), 4,33 (dd, J = 13.6, 3.6 Hz, 1 H), 4,21 (m, 1 H), 4,11 (m, 1 H), 2.98 (m, 1 H), 2.85 (td, J= 13.2, 3.2 Hz, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 1.92 (m, 1 H), 1.83-1.75 (m, 3 H), 1.54-1.35 (m, 2 H); ES+MS: 427 (M+l).

Example Z-8'-
(36,.lla/)-N-f(2,4-.Difluorophenvl)methvl1-6-hvdroxv3-[(l)-l-methvlpropvl]-5,7-dioxo-2.3.5,7,l.l.lla'h-exahvdro[l.3loxazolof3.2-a)pvridofl,2- sodium salt.

The title compound was made in two steps using a similar process to that described in example Z-l. 16a (417 mg, 0.89 mmol) and L-isoleucinol (259 mg, 2.21 mmol) were reacted in 1,2-dichloroethane (40 mL) with acetic acid to give
(36,,lla7i')-N-[(2,4-difluoi'ophenyl)methyl]-3-((l6)-l-methyli)i:op.yl]-5,7-d ioxo"6'[(phenylmethyl)oxy]-2,3,5,7,.ll,.Ua-hexahydro[l,3]oxazolo[3,2-,g]pyrido[l,2-a']pyrazine-8-caL-boxamide (426 mg, 90%). This material was hydrogenated in a second step as described in example Z-l to give
141

(35Jla/e)-7V-[(2,4-Difluorophenyl)niethyl]-6-hydroxy-3-[(l-5)-l-methyipropyl]-5,7-dioxo•2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-,a]pyrido(l,2-c/]pyrazine-8-carboxami(ie (376 rag, 99%) as a coarse white solid. "H NMR (CDCla) 6 11.43 (br, 1 H), 10.27 (br, 1 li), 8.32 (s, 1 H), 7.33 (m, 1 H). 6.79 (m, 2 H), 5.26 (dd, J= 9.6, 4.0 Hz, 1 H), 4.62 (m, 2 H), 4.42-4.35 (m, 2 H), 4.19 (dd, J= 8.8, 7.2 Hz, 1 H), 4.01 (dd, ,/= 8.8, 5.6 Hz, 1 H), 3.86 (dd, /= 12.0, 10.0 Hz, 1 H),~2.27 (ra, 1 H), 1.40 (m, 1 H), 1.15 (m, 1 H), 0.97 (t, J = 7.2 hz, 3 H), 0.91 (d, J= 6.8 Hz, 3 H); ES+ MS: 448 (M+l). This material (360 mg, 0.81 mmol) was treated with sodium hydroxide (0.81 mL, 1.0 M, 0.8.1 mniol) in ethanol (1.5 mL) as described in example Z'1 to provide its corresponding sodium salt (384 mg, 99%) as a white solid. »H NMR (DMSO-oV,) 5 10.82 (m, 1 H), 7.80 (m, l.H), 7.33 (m, 1 H), 7.18 (m, 1 H), 7.00 (in, 1 H), 5.14 (111, 1 H), 4.47 (d, J= 5.6 Hz, 2 H), 4.31 (m, 1 H), 4.18 (m, 1 H), 3.96 (m, 1 H), 3.84 (m, 1 H), 3.71 (m, 1 H), 3.40 (m, 1 H), 1.88 (m, 1 H), 1.36 (m, 1 H), 1.04 (m, 1 H), 0.85 (t, J= 7.2 Hz, 3 H), 0.80 (d, J= 6.8 Hz, 3 H);ES--MS: 448 (M+l).

Example Z'9:
(3',llaye)-N-K2.4-DifluoroBhenvl)methyl1-6-hvdroxv3-methvl-5.7-dioxo-2.3.5.7.1.1.1]-a'hexahydro[l,3]oxazolo[3.2-a1pyrido[l,2-t3']pyrazine-8-carboxamide sodium salt.

The title compound was made in two steps using a similar process to that described in example Z-l. 16a (510 mg, 1.08 mmol) and (25)-2-amino-l-pi'opanol (0.17 mL,
142

2.17 mmol) were reacted in 1,2-dichloroethane (20 mL) with acetic acid to give
(36,,lla/?)-A-{(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,].la-hexahydro[l)3]oxazolo[3,2-]pyrido[l,2-o']pyrazine'8-carboxamide (500 mg, 93%). This material was hydrogenated in a second step as described in example Z-1 to give
35; llai3-A[(2,4-DifluorophenyJ)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,1.1a-hexahydro[l,3]oxazolo[3.2-a]pyrido[l,2-£/]pyrazine-8-carboxamide (386 mg, 94%) as a

tinted white solid. 'H NMII (CDCIs) 6 11.46 (m, 1 H), 10.28 (m, 1 H), 8.32 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.30 (dd, J- 10.0, 4.0 Hz, 1 H), 4.63 (m, 2 H), 4,48-4.37 (m, 3 H), 3.91 (dd, J- 12.0, 10.0 Hz, 1 H), 3.73 (m, 1 H), 1.48 (d, J- 6.0 Hz, 3 H); ES+ MS: 406 (M+I). This material (385 mg, 0.95 mmol) was treated with sodium hydroxide (0.95 mL, 1.0 M, 0.95 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (381 mg, 94%) as a white solid. 'H NMR (DMSO-A) 6 10.66 (m, 1 H), 7.93 (s, 1 H), 7.33 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, .1 H), 5.19 (m, 1 H), 4.59 (m, 1 H), 4.48 (m, 2 H), 4.22 (m, 2 H), 3.75 (m, 1 H), 3.57 (m, 1 H), 1.24 (d, /= 5.6 Hz, 3 H).

Example 2-.1Q:

(35.11.a/f,)-A-f(4-Fluorophenvl)methvl]-6-hvdroxy-3-methvl-5,7-dioxo-2.3.5.7.11.11a-he xalwdrofl,3]oxazolol3,2-a]pyrido[] ,2-cflpvrazine'8-carboxamide.

143

The title compound was made in two steps using a similar process to that described in example Z_2. 16 (100 mg, 0.22 mmo 1) and (26)-2-amino-l-propanol (0.10 mL, 1.28 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (35,,lla./?)-A':((4-fluorophenyl)methyl]-3-methy]-5l7-dioxo-6-[(phenylmethyl)oxy]-2,3,5, 7,IIIIla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-a']pyrazine-8-carboxamide (100 mg, 95%). This material was hydrogenated in a second step as described in example Z"2 to give

(35: lla-A--FluorophenyDmethyll-e-hydroxy-S-methyl-S,7x0-2,3,5,7,11, lla-he xahydro[l,3]oxazolo[3,2-a]pyrido[l,2-o']pyrazine-8-carboxamide (80 mg, 99%) as a white solid. 'H NMR (CDCb) 6 11.43 (br, 1 H), 10.28 (br, 1 H), 8.35 2 H), 6.97 (m, 2 H), 5.29 (m, 1 H), 4.55-4.38 (m, 5 H), 3.89 (apparent t, J = 10.8 Hz, 1 H), 3.70 (m, 1 H), 1.45 (d, J= 5.6 Hz, 3 H); ES" MS: 386 (M-l).

Example Z-.II-

(36", lla)-A-[(2,4-Difliiorophenvl)methvll-3-(l,.l-dimethvlethvl)-6-hvdroxv-5,7-dioxo-2 ,3,G,7,]l,lla-hexahvdro[l,3]oxazolo[3.2-|pyridol l,2-tflpyrazine-8-carboxamide

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (41 mg, 0.09 mmol) and freebased L-tertrleucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (35',lla/e)-N-((2,4-difluorophenyl)methyl]-3-(l,l-dimethylethyl)-5,7-dioxo-6-[(phenylm

144

ethyl)oxy]-2,3,5,7,ll,.Ua-hexahydjo[l,3]oxazolo[3,2-a]pyrido[l,2-<7']pyrai;ine-8-carboxa mide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-2 to give

<3iS,,IlaD-iV-[(2,4-Difluorophenyl)methyl]-3-(l,l-dimethylethyl)-6-hydroxy-5,7-dioxo-2 ,3,5,7,ll,lla-hexahydro[l,3loxazolo[3,2-a]pyrido[l,2-fl']pyrazine-8-carboxamide (33 mg, 99%) as a tinted white solid. »H NMR (CDCla) 5 10.29 (s, 1 H), 8.37 (s, 1 H), 7.34 (m, .1 H), 6.79 (m, 2 H), 5.43 (ra, 1 H), 4.62 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.81 (m, 1 H), 1.03 (s, 9 H); ES- MS: 448 (M+l).

i

Example Z-.12:

(3ff,lla/t,)-3-(l,l-Dimethylethvl)-iV-[(4-fluorophenyl)methYl]-6-hvdroxv-5.7-dioxo-2,3,5. 7.11. ll.a-hexahvdro[l.3]oxazolo[3,2-a]pvrido[l,2-tf]pyrazine-8 earboxamide.

The title compound was made in two steps using- a similar process to that described in example Z-2. 16 (41 mg, 0.09 mmol) and freebased L-fer/l-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (36;ilay?)-3-(l,l-dimethylethyl)-A[(4-fluorophenyl)methylJ-5,7-dioxo-6-[(phenylmethy l)oxy.l-2,3,5,7, llJlla-hexahydro[l,3]oxazolo(3,2-a]pyrido[l,2-fl']pyrazine-8-carboxamide (40 mg, 85%). This material was hydrogenated in a second step as described in example Z-2 to give

(3-S;ila/t:)-3-(l,l-Dimethylethy0-7V-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,

145

7,11, lla-hexahydro[l,3]oxazolo[3,2fl]pyrido[l,2-rf)pyrazine-8-caiboxamide (32 mg, 97%) as a tinted white solid. 'H NMR (CDCls) 6 11.15 (br, 1 H), 10.32 (s, 1 H), 8.38 (s, 1 H), 7.29 (m, 2 H), 6.98 (m, 2 11), 5.43 (m, 1 H), 4.58 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.79 (m, 1 H), 1.02 (s, 9 H); ES+ MS: 430 (M+l).

Example Z-.13:

(3g.lla/e)-A/:f(2.4-Difluorophenvl)methvll-6-hvdroxv-5.7-dioxo-3-nhenyl-2.3.5.7.1Llla •hexahvdrof l,3]oxazolof 3,2-ajpvridot 1,2-flip yrazine-8-carboxarriide.

The title compound vvas made in two steps using a similar process to that described in example Z-2. 16a (33 mg, 0.07 mraol) and L-phenylglycinol (19 mg, 0.14 mmol) were reacted in dichloromethane (2 niL) with acetic acid to give (36;ila7?)-A[(4-fluorophenyl)methyl]-5,7-d ioxo-3-phenyl-6-[(phenylniethyl)oxy]"2,3,5, 7,1 l,lla-hexahydro[l,33oxazolo[3,2 .gJpyridotl-rflpyrazine-S-carboxamide (37 mg, 95%). This material was hydrogenated in a second step as described in example Z~2 to give

(35',lla)-A-[(2,4-Difluorophenyl)niethyll-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,ll,lla -hexahydro[l,3]oxazolo[3,2-]pyrido[l,2-fl']pyi'azine-8-carboxamide (33 mg, 99%) as a tinted white solid. 'H NMR (CDCl3) 6 11.23 (br, 1 H), 10.27 (s, 1 H), 8.39 (s,l H), 7.43-7.32 (m, 6 H), 6.80 (m, 2 H), 5.58 (d, J~ 6.8 Hz, 1 H), 5.37 (apparent t, J= 6.8 Hz, 1 H), 4.67-4.62 (m, 3 H), 4,54 (d, /= 10.4 Hz, 1 H), 4.11 (m, 1 H), 4.01 (m, 1 H); ES*

146

MS--468 (M+l).

Example Z-H-

(36'.1.1.a)-A-[(2,4-DifluoroBhenvl)methvn-6-hvdroxv-3-(hvdroxvmethvl)-5,7-dioxo-2,3,

5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pvridofl.2-(:/IDvrazine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.10 mmol) and

(2/d-2amino-3-[(phenylmethyl)oxy]-l-propanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (35;na/t:)-A[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy] -3- {[(phenyl methyl)oxyjmethyl}-2,3,5,7,ll,lla-hexahydro[l,3]oxazolof3,2-a}pyrido[l,2-o']pyrazine-8-carboxamide (61 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (35,,lla7?)-A-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3, -5,7, ll,lla-hexahydro[l,3]oxazolo[3,2'a]pyrido[l,2-rf]pyrazme-8-carboxamide (37 mg, 87%) as a tinted white solid. iH NMR (CDCI3/CD3OD) 6 8.23 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.31 (d, J- 7.6 Hz, 1 H), 4.56 (s, 2 H), 4.42-4.36 (m, 3 H), 4.17-4.11 (m, 2 H), 3.85 (m, 1 H), 3.62 (d, J= 11.2 Hz, 1 H).

Example Z-1G:

147

(2t,9.3/iD-N-K2.4-Difluorotihenvl)methvn-6-hvdroxv-3-methvl-5.7-diQxo-2-Dhenvi-2,3,5,7 ,11, lla-hexahvdro[l,3]oxa?,olo[3,2-alDvrido[l,2-fl,1pyrazine-8-carboxamide,

The title compound was made in two steps using" a similar process to that described in example Z-2. 16a (25 rag, 0.05 mraol) and (l,2i?)(+)-norephedrine (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (26',3/?)-Af[(2,4-difluorophenyl)methyl'J-3-methyl-5,7-dioxo-2-phenyl-6-[(phenylmethyl) oxy]-2,315,7,ll,lla-hexahydro[l,3]oxazolo[3,2a]pyrido[lJ2-f/]pyrazine-8-carboxamide (30 nig, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (26,)3it')-Ar-[(214-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-213)557, ll,].la-hexahydro[l,3]oxazolo[3,2-<3]pyrido{l,2-rf]pyrazme-8-carboxamide (25 mg, 91%) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center). 'H NMR (CDCl3/CD3OD) 6 10.28 (m, 1 H), 8.38 (s, 1 H), 7.10-7.30 (m, 6 H), 6.78 (m, 2 H), 5.70 (d, J= 7.6 Hz, 1 H), 5.36 (d, J= 5.2 Hz, 1 H), 4,82 (m, 1 H), 4.61 (m, 2 H), 4,47 (d, 10.4 Hz, 1 H), 4,00 (apparent t, J= 10.4 Hz, 1 H), 0.94 (d, J= 6.4 Hz, 3 H); ES+ MS:

482 (M+l).

Example Z-16:

(3./g,lla6!)-N-K2,4-Difluoropheuvl)methvll-6-hvdroxv-5,7-dioxo-3-(phenvlmethvl)-2.3,5.

148

7,ll,lla-hexahydro[J.,3loxazolo[3,2-alDvridofl.2-(Tr1pyrazine-8-carboxamide

The title compound was made in two steps using a similar process to that described in example Z-2, 16a (34 mg, 0.07 mmol) and (2i2)-2-amincr3-phenyl-l-pi-opanol (D-phenylalaninol) (50 mg, 0.33 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (Sli, llai.?lAr-[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethy l)oxy]-2,3,5,7,ll,llahexa]iydio[l,3.]oxazolo[3)2-a]pyrido[ll2-']pyrazine-8-carboxamide (29 mg, 70%). This material was hydrogenated in a second step as described in example Z"2 to give (3E,1 la6)-7V-[(2,4-Dif'luorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3)5, 7,ll,lla-hexahydro[] ,3]oxazolot3,2-a]pyrido[l,2-a']pj'razine-8-carboxamide (24 mg, 98%) as a white solid. >H NMR (CDCla) 5 11.46 (br, 1 H), 10.27 (m, 1 H), 8.33 (m, 1 H), 7.32-7.16 (m, 6 li), 6.78 (m, 2 H). 5.02 (m, 1 H), 4.61 (m, 3 H), 4,39 (m, 1 H), 4,22 (m, 1 H), 3.95 (m, 1 H), 3.87 (m, 1 H), 3.36 (m, 1 H), 2.97 (dd, J= 13.2 8.8 Hz, 1 H); ES" MS:482(M+1).

Example ZJ.7:

(3/,lla6)-N-f(2,4-DifluoroDhenvl)methvl1-6-hvdroxv-3-(2-methvlproDvl)-5,7-dioxo-2.3. G,7,ll,lla-hexahvdro[l,3]oxazolo[3,2-a1pyridofl,2-fl']pvrazine-8-carboxamide.

149

The title compound was made in two steps using a similar process to that described in example Z'2. 16a (32 rag, 0.07 mmol) and (272)-2-amino-4-methyl-l-pentanol (0.1 mL) were reacted in dichlorome thane (2 mL) with acetic acid to give (3R,llaS)-N- [(2,4-difluorophenyl)methyl]-3-(2-methylpropyl)-5,7-dioxof)-t(phenylmeth yl)oxy]-2,3,5,7,ll,lla-hexahydrofl>3]oxazolo[3,2-,?3]pyrido[l,2-a']pyrazine-8-carboxamid e (43 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3/i?/lla.S)-7V:t(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3, 5,7,l].,lla-hexahydroU,3]oxazolo[3,2-a]pyridofl,2-J]pyrazine-8-carboxamide (32 mg, 90%) as a white solid. 'H NMR (CDCla) 5 11.47 (br, 1 H), 10.29 (m, 1 H), 8.35 (s, 1 H), 7.39 (m, 1 H), 6.80 (m, 2 H). 5.31 (m, 1 H), 4.62 (m, 2 H), AAA (m, 2 H), 4.37 (m, 1 H), 3.88 (m, 1 H), 3.84 (dd, J= 8.0, 5,6 Hz, 1 H), 2.04 (m, 1 H), 1.62 (m, 1 H), 1.41 (m, 1 H), 1.00 (d, /= 5.6 Hz, 3 H). 0.99 (d, /= 6.0 Hz, 3 H); ES+ MS: 448 (M+l).

Example Z-18:

(5aiZ.14a)-Af(2,4-Difluoronhenvl)methvll-11-hydroxy 10,12-dioxo-1,2.3.4.5a,6,.10,12. 14,14a'decahvdropvrido[l.2-a]pyridof.r.2':3.4]imidazoll,2-fl>lpyrazine-9-carhoxamide.

150

a) 1,1-Dimethylethyl (2/$-2-(aminocarbonyl)-l-piperidinecarboxylate. To a cold (0 °C) solution of (2/f)-l{[(l,l-dimethylet-.hyl)oxy]carbonyl}-2-piperidinecarboxylic acid (1.0 g, 4.36 mmol) in THF (20 mL) was added triethylamine (0.60 ml, 4.36 mmol) followed by slow addition of methyl chloroformate (0.34 mL, 4,36 mmol). After a few minutes a suspension had formed. To this mixture was added concentrated NKUOH

minutes a suspension had formed. To this mixture was added concentrated NH4OH (1.5 mL) and the solution was allowed to warm to rt as the bath warmed and stirred for a total of 4 h. The mixture was concentrated in vacuo and the residue was taken up in EtOAc, The organic layer was washed with citric acid, bicard and then hrine, dried over NaaSO-i. Filtration and concentration gave 1,1-dimethylethyl (2i?)-2-(aminocarbonyl)-l-piperidinecarboxylate (1.0 g, 99%). 'H NMR (CDCL) 6 6.03 (br, 1 H), 5.45 (br, 1 H), 4.77 (br, 1 H), 4,06 (br, 1 H), 2.82 (m, 1 H), 2.29 (m, 1 H), 1.67-1.43 (m, 13 H).

b) 1,1-Dimethylethyl (2ii!)-2-cyano-l-piperidinecarboxylate. To a cold (0 °C) solution of 1,1-dimethylethyl (2./?)-2-(aminocarbonyl)-l-pipet-idinecarboxylate (269 mg, 1.17 mmol) in THF (10 mL) was added triethylamine (0.33 mL, 2.34 mmol) and then trifluoroacetic anhydride (0.17 mL, 1.17 mmol). The mixture was stirred at 0 °C for 1 h and concentrated in vacuo. The residue was taken up in EtOAc and washed successively with sodium bicarbonate, 0.5 AHCl and brine. The organics were dried over NaaSO-i, filtered and concentrated to give 1,1-dimethylethyl (2/t3-2-cyano-l-piperidinecarboxyiate (255 mg, 99%) as a crystalline solid upon standing. >H NMR (CDCla) 5 5.23 (br, 1 ll), 4,05 (br, 1 H), 2.93 (br, 1 H), 1.93-1.39 (m, 6 H), 1.46 (s, 9 ll).

151

c) 1,1 "Dimethylethyl (27(?)-2-(aminomethyl)-l-piperidinecarboxylate. An ammonia saturated ethanol solution of 1,1-dimethylethyl (272)-2cyano-l-piperidinecarboxylate (255 mg, 1.19 mmol) was reduced with RaneyNi in a similar manner to that described in example Z-3 to give after filtration through a short plug of silica, 1,1-dimethylethyl (2i?)-2-(aminomethyl)-l-piperidiuecarboxylate (236 mg, 91%), as an oil. "H NMIt (CDCla/CDaOD) 5 4.15 (br, 1 H), 3.97 (m, 1 h), 2.96 (m, 1 H), 2.75-2.69 (m, 2 H), 2.23-2.08 (m, 3 H), 1.59-1.55 (m, 3 H), 1.43 (s, 9 H).

d) t(2iZ)-2-Piperidinylmethyl]amine bis HC1 salt. A solution of 1,1-dimethylethyl (2/i!)-2-(aminomethyl)-l-piperidinecarboxylate (236 mg, 1.08 mmol) in THF (10 mL) was treated with 4 NKC\ (3 mL) as described in example Z-3 to give the bis HC1 salt of[(2/a-2-Piperidinylmethyl]amine. >H NMR (DMSO-tfe) 6 9.67 (br, 1 H), 9.48 (br, 1 H), 8.48 (br, 2 H), 3.70 (br, 2 H), 3.20 (m, 1 H), 3.04 (m, 1 H), 2.86 (m, 1 H), 1.89-1.41 (m, 6 H).

e)

(5a,14a/2)-AA-((214-Difluorophenyl)methyl]-ll-hydroxy-10,12-dioxo-l,2,3,4,5a,6,10,12, 14114a-decahydropyrido[l,2-<3]pyrido[r,2':3,4]imidazo[l,2-rf]pyrazine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.11 mmol) and [(2iS)-2-Piperidinylmethyl]amine (150 mg, 1.31 mmol) (free based using carbonate resin as described in example Z'3) were reacted in dichloromethane (2 mL) with acetic acid to give

152

(5a, 14ai?)-N-[(2,4-difluoropheiiyl)methyl]-10,12-dioxo-ll-[(phenylmethyl)oxy]-1,2,3,4 ,5a,6,10,12,14,14a-decahydropyrido[l,2-a]pyrido[l',2':3,4]imidazo[l,2-rf]pyrazine-9-car boxamide (50 mg, 88%). This material was hydrogenated in a second step as described in example Z'2 to give

(5ai?,14a/i9-N[(2,4-difluorophenyl)methyl]-ll-hydroxy-10,12-dioxo-l,2,3,4,5a,6,10,12, 14,14a'decahydropyrido[l,2-a]p}a-ido[l',2,;3,4]imidazo(l,2-fl"]pyrazine-9-carboxamide (11 mg, 44%) as a white solid, 'H NMR (CD3OD/CDCl3) 5 10.46 (m, 1 H), 8.32 (s, 1 H), 7.31 (m, 1 H), 6.80 (m, 2 H), 4.64-4.52 (m, 3 H), 4.14 (dd, J= 10,4, 2.8 Hz, 1 H), 3.91-3.82 (m, 2 H), 3.19 (apparent:t, J= 10.8 Hz, 1 H), 3.08 (d, J= 10.4 Hz, 1 H), 2.50 (m, 1 H), 2.27 (m, 1 ll), 1.99-1.30 m, 6 H); ES* MS: 445 (M+l).

Example Z~ 19:

(2,36!)-A[(2,4-Difluorophenvl)methvl1-6-hvdroxy-3-f(methvloxv)niethvl1-5,7-dioxo-2-p henvl-2,3,5,7.1.1,lla-hexalivdro[l,3]oxazo]o[3,2-fl]pvrido[l,2-(/|pyrazine-8'carboxamide

The title compound was made in two steps using a similar process to that described in example Z'2. 16a (36 mg, 0.07 mmol) and (2/i!)-2-amino-4-methyl-l-pentanol (0.1 niL) were reacted in dichloromethane (2 mL) with acetic acid to give

(26',35)-7vr-[(2,4-difluorophenyl)methyl]-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-6-[(p henylmethyl)oxy]-2,3,5,7,II,IIa-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-rflpyrazine-8-c

153

arboxamide. This material was hydrogenated in a second step as described in example Z-2 to give

(25',35)-A'-[(2,4-Difluoropheny])methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2p henyl-2,3,5,7,II,IIa-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-fl']pyrazine-8-carboxamide (25 mg, 64% for 2 steps) as a white solid. This material is a single diastereomer (>6:i diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center). 'H NMR (CDCla) 6 1.1.48 (br, 1 H), 10.30 (m, 1 H), 8.39 (s, 1 H), 7.39-7.24 (m, 6 H), 6.78 (m, 2 H), 5.46 (dd, J= 10.0, 3.6 Hz, 1 ll), 5.33 (d, 2 H), 4,54 (dd, J= 12.4, 4.0 Hz, 1 H), 4.19 (m, 1 H), 4.12 (dd, J= 10.4, 3.2 Hz, 1 H),
4,06 (m, 1 H), 3.55 (dd, J= 10.4, 1.6 Hz, 1 H), 3.40 (s, 3 H); ES+ MS-' 512 (M+l).

Example Z-2Q:

(36'.lla./e)-3-(Cvclohexvlmethyl)-A-f(2,4-difluorop henyl)methvl]-6-hydroxv5.7'dioxo'2, 3,5,7,11,11a-hexa hydro [l,3loxazolo[3,2-a]pyrido[1,2-(ylpyra-zine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z"2. 16a (36 mg, 0.08 mmol) and (2i5)-2-amino-3-cyclohexyl-.l-propaiiol (30 mg, 0.19 mmol) were reacted in dichloromethane (2 raL) with acetic acid to give (3S, lla/i?)-3-(cyclohexylmethyl)-Ar-[(2,4-difluorophenyl)methylj-5,7-dioxo-6-[(phenylme thyl)oxy]'2,3,5,7,II,lla-hexahydro(l>3]oxazolo[3,2a]pyrido[l,2-n']pyrazine-8-carboxa mide (27 mg, 61%). This material was hydrogenated in a second step as described in

154

example Z-2 to give

(3S, lla)-3-(cyclohexylmethyl)"A/'-[(2,4-difluorophenyl)methyl.]-6-hydroxy5,7-dioxo-2,
3,5,7,11, lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-a']pyrazine-8'carboxainide (25 mg,
99%) as a white solid. iH NMR (CDCls) 5 11.48 (br, 1 H), 10.28 (s, 1 H), 8.33 (s, 1 H),
7.33 (m, 1 H), 6.78 (m, 2 H), 5.29 (m, 1 H), 4.61 (m, 2 H), 4.47-4.33 (m, 3 H), 3.87-3.81
(m, 2 H), 2.05 (m, 1 H), 1.75-1.64 (m, 6 H), 1.39 (m, 1 H), 1.25-1.14 (m, 3 H), 1.02-0.97
(m, 2 H); ES+ MS: 488 (M+l).
Example Z-21:
(3r.llaJ?)-iV-[(2.4-DifluoroDhenvl)methvl]-6-hvdroxv-3-(l-methvlethvl)-5.7-dioxo-2,3,5,
7.1.1,lla-hexahvdrofl.3]oxazolo[3.2-a]pvrido[l.2-t/]pvrazine-8cai-boxamide.

The title compound was made in two steps using a similar process to that described
in example Z-l. 16a (42 mg, 0.09 mmol) and (2»5)-2-amino-3-methy]-l-butanol (0.1
raL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give
(36,,lla7?)-Ar-[(2,4-difluorophenyl)methyl]-3-(lmcthylethyl)-5,7 -dioxo-6-[(phenylmethy
l)oxy]-2,3,5,7, ll,lla-hexahydro[l,3joxazolo[3,2a]pyrido[l,2-£/]pyrazine-8carboxamide
(40 mg, 86%). This material was hydrogenated in a second step as described in
example Z-l to give
(35',i:ia)-7V-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-(l-methylethy])-5,7-dioxo-2,3,5,
V.ll.lla-hexahydroll.SjoxazolotS-flJpyridoll-fl'lpyrazine-S-carboxamide (34 mg,
155

99%) as a white solid. 'H NMR (CDCLJ) 6 10.29 (br, 1 H), 8.36 (s, 1 H), 7.33 (m, 1 H),
6.79 (m, 2 H), 5.29 (d, J= 6.4 Hz, 1 H), 4.61 (m, 2 H), 4.44 (d, 1 H), 4.17 (m, 1 H), 4,02 (dd, J= 8.4, 5.2 Hz, 1 H),
3.86 (m, 1 H), 2.37 (m, 1 H), 0.97 (m,
6H); ES- MS:434(M+1).
Example Z-22:
(5aJ.4a6)-Ar-f(2,4-.Difluorophenvl)methvl]-12-hvdroxvll,13-dioxo-5a.6a,7,ll,13,14a-
hexahvdi-o-5N-iiideno(r,2'-4,5][l,3]oxa2olo[3,2-a.lpyrido[l,2-g']pyrazine-.10'carboxamid

The title compound was made in two steps using a similar process to that described
in example Z"l. 16a (42 mg, 0.09 mmol) and
(IS,2R)- l-amino-2,3-dihydro-l.#-inden-2-ol (100 mg, 0.67 mmol) were reacted in
1,2-dichloroethane (5 inL) with acetic acid to give
(5a7?,14a6)-jV-[(2,4-difluorophenyl)methyl]-ll,13-dioxo-12-[(phenylmethyl)oxy]-5a,6a,7
,.ll,13,14a-hexahydro-5y/-indenolr,2':4,5][l,3joxazolo[3,2va]pyridofl,2-a']pyrazine-10-c
arhoxamide (55 mg, 99%). This material was hydrogenated in a second step as
described in example Z~l to give
(5a/i,14a6)-Af[(2,4-difluorophenyl)methyl]-12-hydroxy-ll,13-dioxo-5a,6a,7,.ll,13,14a-
hexahydro-5.ic/'-indeno[r,2':4,5][l,3]oxazolol3J2-]pyrido[l,2-a']pyrazine-10-carboxamid
e (45 mg, 97%) as a white solid. 'H NMR (CDCl.i) 5 10.28 (m, 1 H), 8.33 (s, 1 H),
156

7.69 (d, ,/= 7.2 Hz, 1 H), 7.34-7.19 (m, 4 H), 6.78 (m, 2 H), 5.96 (d, J= 6.0 Hz, 1 H),
5.32 (m, 1 H), 5.22 (m, 1 H), 4.60 (m, 2 H), 4,45 (d, J= 9.2 Hz, 1 H), 3.96 (apparent t, J
= 10.8 Hz, 1 H), 3.40 (dd, /= 18.0, 6.8 Hz, 1 H), 3.24 (d, J = 17.6 Hz, 1 H);); ES
MS: 480 (M+l).
Example 2-23 & Z-24:
(25',3,lla6)-A[(2,4-Difluorophenvl)methvl)-6-hvdroxv-5,7-dioxo-2,3-diphenvl-2,3,5.7,
ll.lla-hexalivdrofl,3loxazolof3.2- (25,.3/gJ.la79-Ar(2,4-difluoropheiiv])methvll-6-hydroxv-5,7-dioxo-2,3-
di.phenvl-2,3,5,7,
ll.lla'hexahvdix>ri.3loxazolof3.2-a1pvridoh..2-a1pvrazine'8-cai,boxarmde.

The title compounds were made in two steps using' a similar process to that
described ;in example Z-l. 16a (40 mg, 0.09 mmol) and
(liS',2)-2-amino-ll2-diphenylethanol (50 mg', 0.23 mmol) were reacted in
1,2-dichloroethane (5 mL) with acetic acid to give
(26;3/?,lla)-A[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)
157

oxyh2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-dpyrido[l,2-dpyrazine-8-carboxamide
(34 rag, 63%) and
(26,,3,lla7i!')-7V-[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-dipheny]-6-((phenylmethyl)
oxy]-2,3,5,7,ll,lla-hexahydro[l,3]oxazo]o[3,2-a]pyrido[l,2'rf]pyrazine-8-carboxamide
(13 mg, 24%). These materials were hydrogenated in a second step as described in
example Z-l to give
(21S,,37?,lla6)N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,
ll>lla-hexahydro[l,3]oxazolo[3l2-a]pyrido[l'.,2-n']pyrazine-8-carboxamide (example
Z-23, 29 mg, 99%) as a white solid and
(25,,3i?,lla)-7V-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,
ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-fl']pyrazine-8-carboxamide (example
Z-24, 10 mg, 89%) as a white solid respectively. For example Z-23: iH NMR
(DMSO-A) 6 10.29 (t, J= 5.6 Hz, 1 H), 8.55 (s, 1 H), 7.38 (m, 1 H), 7.22 (m, 1 H),
7.11-6.95 (m, 11 H), 6.16 (dd, J= 10.4, 3.6 Hz, 1 H), 5.71 (m, 2 H), 4.90 (m, 1 H), 4,54
(m, 2 H), 4,38 (t, J= 11.2 Hz, 1 H); ES' MS-' 544 (M+l). For example Z-24-' 'H NMR
(CDCla) 6 11.64 (br, 1 H), 10.30 (s, 1 H), 8.45 (s, 1 li), 7.34 (m, 1 H), 7.01-6.90 (m, 10
H), 6.80 (m, 2 H), 5.56 (m, 2 II), 5.42 (d, J= 6.4 Hz, 1 H), 4,73 (m, 1 H), 4.63 (m, 2 H),
4.49 (m, 1 H); ES' MS: 544 (M+l).
Example Z-25-"
(3.,lla6)-A-K2,4-Difluorophenvl)methvll-6-hvdvoxv3-(l-methvlethyl)-5,7-dioxo-2,3,5,
7, ll,lla'hexahydro[l,3]oxazolo[3,2'fl]i3vridofl,2-rflpyrazine'8'carboxamide.
158

The title compound was made in two steps using a similar process to that described
in example Zl. 16a (40 mg, 0.09 mmol) and (2A,)-2amino-3-methyM-butanol (0.1
mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give

mL) were reacted in 1,2-dichloroethane (8 mU with acetic acid to give
(3/tf,lla6)-Ar-[(2.4-difluorophenyl)methyl]-3-(l-methylethyl)-5l7-dioxo-6-[(phenylmethy
])oxy]-2,3,5,7,11, lla-hexahydro{l)3)oxazolo[3;2-a]pyridoll,2o']pyrazine-8-carboxamide
(41 mg, 92%). This material was hydrogenated in a second step as described in
example Z'l to give
(37i',lla5)-A'-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(l-methylethyl)-5,7-dioxo-2,3,5,
7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-rflpyi"azine-8-cai-boxamide
(32 mg, 94%) as a white solid. H NMR (CDCb) 8 11.42 (br, 1 H), 10.27 (br, 1 H),
8.34 (s, 1 H), 7.31 (m, 1 H), 6.78 (m, 2 H), 5.28 (d, (m, 1 H), 4,33 (m, 1 H), 4.16 (m, 1 H), 4.01 (dd, J= 8.8, 5.2 Hz.
.1 H), 3.85 (m, 1 H),
2.37 (m, 1 H), 0.97 (d, J= 6.8 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H); ES+ MS: 434
(M+l).
Example Z'26
(36Ulaii')-7vr-K2.4-Difliiorophenvl)methvl]-6-hvdroxv-3-l2-(methvlthio)ethvl]-5,7-dioxo-
2.3,5,7,ll,lla-hexahvdro[l,3]oxazolo[3,2-a]pvrido[l.2- 159

The title compound was made in two steps using a similar process to that described
in example 7,-1. 16a (43 mg, 0.09 mmol) and (2$-2-amino-4--(methylthio)-] -butanol
(0.1 mL) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give
(311a-A[(2,4-difliiorophenyl)methyl]-3-[2-(methylthio)ethyl]-G,7-dioxo-6-[(phenyl
methyl)oxy]-2,3,5,7,ll,lla-hcxahydro[l,3]oxazolo[3,2-a]pyrido[l,2-f/]pyrazinc-8-carbox
amide (41 mg, 81%). This material (20 mg, 0.04 mmol) was treated with
trifluoroacetic acid (l mL) in dichloromethane (3 mL) at 0 °C to rt over 6 h. The
mixture was concentrated in vacuo and subjected to reverse phase preparative HPLC
purification to provide
(311a/i5-A4'(2/lT)ifluoropheny])methylJ-6-hydrox.y-3-(2-(methylthio)ethyl]-5,7-dioxo-
2,3,5,7,ll,lla-hexahydi'o[l,3]oxazo]o[3,2-a]pyi*idoll12-rflpyrazine-8-carboxamide
(12 mg, 72%) as a white solid. . 8.34 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.32 (in, 1 H). 4.62-4.53 (m, 3 H), 4.43-
4.39
(m, 2 H), 3.91-3.87 (m, 2 H), 2.63-2.53 (m, 2 H), 2.39 (m, 1 H), 2.12 (s, 3 H), 1.89 (m, 1
H); ES' MS: 466 (M+l).
Example Z-27

(35,,lla./g)-7V1[(2,4-Difluorophenvl)me(:hvl]-6-hvdroxv-3-f2-(methvlsulfonvl)ethvl.]-5,7-di
oxo-2.3,5,7,ll,lla-hcxahvdro[l,3]oxazolo[3,2-r73pvrido[l.2 160

To a solution of
(36;ila)-VV'-f(2>4-difiuorophei-iyl)ineth}d]-3-l2-(raethylthio)ethyl]-5,7-dioxo-6-((phenyl
methyl)oxy]-2,3,5,7, ll,lla-hexahydro[l,3]oxazolot3,2-a3pyrido[l,2-a']pyrazine-8-carbox
amide (20 mg, 0.04 mrnol) in dichloromethane (5 mL) at 0 °C was added JWCPBA (20
rag, 70%, 0.082 mmol). The resultant solution was allowed to warm as the bath
warmed and stirred a total of 3 h. The reaction was quenched ly the addition of
Na2S203 (aq) and sodium bicarbonate. The layers were separated and the organic
layer washed with brine. The aqueous layer was extracted with dichloromethane
and the combined organics dried over NasSO-i. Filtration and concentration provided
(35;ila7?)-Ar-[(214-difiuorophenyl)methyl.l-3-l2-(methylsulfonyl)ethyl]-5,7-dioxo-6-[(phe
nylmethyl)oxy]-2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-]pyridofl12-fl']pyrazine-8-car
boxamide (26 mg, 99%) as a white solid. This material was hydrogenated in a second
step as described in example Z-l to give
(36;ila)-A[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-di
oxo-2,3,5,7,11, lla-hexahydro[l,3]oxazolo[3,2-tf]pyrido[l,2-a']pyrazine-8-carboxamide
(22 mg, 99%) as a white solid. H NMR (CDCla) o 11.00 (br, 1 H), 10.16 (s, 1 H), 8.33
(s, 1 H), 7.36 (m, 1 H), 6.81 (m, 2 H), 5.42 (m, 1 H), 4,62 (m, 3 H), 4.41 (m,2 H), 3.93
(m, 2 H), 3.31 (m, 2 H), 2.98 (s, 3 H), 2,40 (m, 1 H), 2.28 (m, 1 H); BS+ MS: 498 (M+l).
Example Z-28-'
161

(36'Jla.J?)-N-[(2,4-Difli)orophenvl)mcthyl]-6-hydroxv-3-(3N-indol-3-vlmethvl)-5,7-dioxo
-2,3,5,7,ll,lla-hexahvdi-ofl.3loxazolo[3.2-a1t)vrido[l,2-a1pvrazine-8-carboxamide.
H
l l H
The title compound was made in two steps using a similar process to that described
in example Zl. 16a (43 mg, 0.09 mmol) and
(26)"2-amino-3"(IN:indol'3-yl)-l-propanol (100 mg, 0.52 mmol) were reacted in
1,2-dichloroethane (5 mL) with acetic acid to give
(35; lla/9-A-[(214-difluorophenyl)methyl]-3-(l.ff'-indol-3-ylniethyl)-517-dioxo-6-[(phenyl
methyl)oxy]-2,3,5,7, ll.lla-hexahj'droflJSjoxazolotS-aJpyridofl-rflpyrazine-S-carbox
amide (36 mg, 64%). This material was hydrogenated in a second step as described
in example 7,-1. to give
(35;].la/3-N-[(2,4-.Difluoropheny])methyl]-6-hydroxy-3-(l/indol-3-ylmethyl)-5,7-dioxo
-2,3,5l7,ll,lla-hexahydro[l.,3]oxazolof3,2-/?]pyrido[l,2-fl']pyrazine-8-carboxamide (29
mg, 95%) as a white solid. 'H NMR (CDCl3/CD3OD) 6 10.34 (m, 1 li), 8.98 (br, 1 H),
8.24 (s, 1 H), 7.58 (d, J= 8.0 Hz, 1 H), 7.32 (m, 2 H), 7.15-7.01 (m, 3 H), 6.78 (m, 2 H),
4.94 (d, /= 6.8 Hz, 1 H), 4.7.1 (d, J= 5.6 Hz, 1 H), 4.59 (m, 2 H), 4.35 (d, J= 10.4 Hz, 1
H), 4.22 (in, 1 H), 3.99 (m, 1 H), 3.81 (m, 1 H), 3.40 (dd, J = 13.6, 11.6 Hz, 1 H), 3.18
(dd, J= 14,0, 8.4 Hz, 1 H); E.S+ MS: 521 (M+l).
Example Z-29:
(4/)J, 3 2aig)-Ar-|(4-fluorophenvl)methvl]-7-hvdi-oxv-4-methvl-l-(2-mcthvlpror)vl)-6.8-diox
162

o-1..2.3.4,6,8,12,12a-octahvdropvridolr.2'.4.5lpvrazinoll,27]pvrimidirie-9-carboxamid

a) (2/)-2-({[(l,l-Dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate. To a
stirred solution of 1,1-dimethylethyl [(.li?)-2-hydroxyl-methylethyl]carbamate (5.00 g,
28.5 mmol) and triethylamine (5.92 mL, 42.9 mraol) in CH2Cl2 (30 mL) cooled to 0 °C

and under a nitrogen atmosphere was added dropwise a solution of methanesulfonyl chloride (2.43 mL, 31.5 mmol) in CH2Cl2 (25 mL). Stirring was continued for 20 minutes at 0 °C, after which time the reaction was judged complete by TLC analysis (l'l hexanes/EtOAc). The solution was poured into water and the layers were

separated. The organic phase was washed with 0.1 N HC1 and then with 5% NaHCOa, dried over Na2SO-f, filtered and concentrated to give (2/d'2-({[(l,l-dimethylethyl)oxyJcarbonyl}amino)propyl methanesulfonate (7.08 g, 98%) as a white solid. W NMR (400 MHz, CDCU) 8 1.23 (d, J= 6.8 Hz, 3H), 1.44 (s, 9H), 3.03 (s, 3H), 3.97 (m, IH), 4.15 (dd, J= 4,2, 9.8 Hz, 1H). 4.21 (m, 1H). 4.6.1 (br s, 1H).
b) 1,1-Dimethylethyl l(lJ?)-2-cyano-l-methylethyl]carbamate. To a stirred solution of (2ZZ)-2-({[(l,l-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (7.08 g, 27.9 mmol) in DMSO (50 mL) was added NaCN (3.78 g, 84,0 mmol). The solution was stirred at 70 °C for 2 hours, over which time the formation of a precipitate was
163

observed. After cooling at room temperature, water was added and the mixture was extracted with Et-'O. The ethereal layers were washed with a brine solution, dried over Na2SO'i, filtered and concentrated to give 1,1- dime thylethyl [(l/£)-2-cyano-l-methylethyl]carbamate (3.81 g, 73%) as a pale yellow solid. IH NMR (400 MHz, CDC13) 8 1.30 (d, J= 6.8 Hz, 3H), 1.42 (s, 9H), 2.51 (dd, J= 3.8, 16.6 Hz, 1H), 2.73 (m, 1H), 3.93 (m, 1H), 4,63 (br s, 1H).
c) 1,1-Dimethylethy] [(l./?)-3-amino-l-methylpropyl]carbamate. A solution of 1,1-dimethylethyl [(l/i9-2-cyano;l-methylethyl]carbamate (1.30 g, 7.1 mmol) in etlianol saturated with anhydrous ammonia was treated with Raney-Ni (1.5 mL of 50% aq. Suspension) and 55 psi of H2 overnight. The mixture was filtered through Celite and the filtrate Avas concentrated in vacuo. The residue was purified by flash chromatography (80U9:i CH2Cb/MeOH/Nl-LjOH (37%) gradient elution) through a short plug of silica gel to give 1,1-dimethylethyl f(l/9-3amino-l-methylpropyl]carbamate (1.37 g, 100%) as a clear oil that solidified. >H NMR (400 MHz, CDCl3) 6 1.14 (d, J= 6.8 Hz, 3H), 1.43-1.62 (m, 13H), 2.76 (m, 2H), 3.77 (m, 1H), 4.57 (in, Hi).
d) 1,1-Dimethylethyl {(!/£>-l-methyl-3-((2-methylpropyl)amino]propyl}carbamate. 1,1-dimethylethyl ((l./3-3-amino-1 mcthylpropyl]carbamate (0.320 g, 1.70 mmol), isobutyraldehyde (150 pL, 1.62 mmol), and sodium triacetoxyborohydride (0.512 g, 2.4 2 mmol) were stirred in anhydrous dichloroethane (10 mL) at ambient temperature overnight. The reaction was quenched by the addition of saturated NaHC03 and
164

then extracted with dichloromethane. The combined extracts were washed with water, dried over Na2SO-i, filtered and concentrated. The residue was purified by flash chromatography (80:19a CHaCla/MeOH/NH-iOH (37%) gradient elution) through a short plug of silica gel to afford 1, l''dimethylethyl {(l7i?)-l-methyl-3-[(2-methylpropyl)aminoJpropyl)carbamate (0.158 g, 40%) as a clear oil. 'H NMR (400 MHz, CDCla) 6 0.90 (d, J= 6.4 Hz, 6H), 1.13 (d, /= 6.4 Hz, 3H), 1.42-1.51 (m, 11H), 1.67-1.75 (m, 2H), 2.33-2.42 (m, 2H), 2.58-2.72 (m, 2H), 3.72 (m, 1H), 5.20 (m, 1H).
e) f(3/d-3-Arninobutyl](2-methylpropy0amine. An ice cold solution of 1,1-dimethylethy 1 {(1 B)l-methyl-3-[(2-methylpropyl)amino]propy 1}carbamate (0.158 g, 0.65 mmol) in THF (8 mL) was treated with 4 7VHC1 (aq) (2 mL) and then stirred at room temperature for 2 h. The mixture was concentrated in vacuo to give [(3/?)-3-aminobvityl](2-methylpropyl)amine dihydrochloride. The HC1 salt was then dissolved in dichloromethane and a minimal amount of methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies). After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully in vacuo to give [(3./$-3-aininobutyl](2-methylpropyl)aminc (65 mg). 'H NMR (400 MHz, CDCLs) S 0.88 (d, J= 6.0 Hz, 6H), 1.06 (d, /= 5.6 Hz, 3H), 1.231.53 (m, 5H), 1.71-1.74 (m, 1H), 2.39 (m, 2H), 2.65 (m, 2H), 2.97 (m, 1H).
f)
(4/?,12a72)-A'-l(4-Fluorophenyl)methylJ-7-hydroxy-4-inethyl-l-(2-methylpropyl)-6,8-dio
165

xo-l,2,3,4,6,8,12,12a-octahydropyridolr,2':4,5]pyrazino[l,2-a]pyi-imiciine-9-carboxami de. The title compound was made in two steps using a similar process to that described in example Z"2. 16 (40 mg, 0.09 mmol) and ((3i?)-3-aminobutyl](2-metliylpropyl)amine (65 mg, 0.45 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4/e,12a')-A';[(4-fluorophenyl)methyl]-4-methyl-l-(2-methylpropy])-6,8-dioxo-7-[(phen ylmethyl)oxy]-l,2,3,4,6,8J.2,12a-octahydropyridoll',2'-'4,5]pyrazino[l,2-a.]pyrimidine-9 -carboxamide (29 mg, 60%). This material was hydrogenated in a second step as described in example Z-2 to give (4./?, 12ai2)-A':[(4-fluorophenyl)meth34]-7-hydroxy'4-methyM-(2-methylpropyl)-6,8-diox o- l,2,3,4,6,8,12,12a-octahydropyrido[r,2'-4,5]pyrazino[l,2-a]pyrimidine-9-carboxamid e (18 mg, 75%) as a tan solid. 'H NMR (400 MHz, CDCls) 8 0.77 (d, ,/= 6.4 Hz, 3H), 0.84 (d, ,/ = 6.4 Hz, 3H), 1.32 (d, J= 7.2 Hz), 1.45-1.49 (m, 1H), 1.57-1.67 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m,*lH), 2.73-2.79 (m, 1H), 2.87-2.92 (m, 1H), 4.16-4.24 (m, 2H), 4.45 (s, 1H), 4.54-4.64 (m, 2H), 4.96-4.99 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.46 (s, IH), 12.55 (s, 1H); ES+ MS: 456 (M+l).
Example 23Q:
(4ig.l2a)-A-K4-Fluorophenvl)methv]]-7-hvdroxv-4-methvl-l-(3.-methvlethyl)-6,8-diox o-1.2.3.4.6,8.12,1.2a-octahvdropyrido[r.2':4,5lpvrazinoll,2v?]pyrimidiiie-9-carboxamid e
166

a) [(3/i)-3-Aminobu(.yl](l-methylethyl)amine. The free diamine was prepared in a similar manner as described in example Z-29. 'H NMR (400 MHz, CDCIs) 8 1.04 (d, /= 6.4 Hz, 6H), 1.06 (d, J = 6.4 Hz, 3H), 1.41-1.58 (m, 5H), 2.62-2.66 (m, 2H), 2.74-2.80 (m, 1H), 2.92-3.00 (m, 1H).
b)
{AR, 12a72)-7V-[(4-.Fluorophenyl)methyl]-7-hydroxy-4-methyM-(l-methylethyl)-6,8-diox o-l>2,3,4,6,8,.12,12a-octahydropyrido[l',2';4,5]pyrazino[l,2-]pyrimidine-9-carboxamid e. The title compound was made in two steps vising a similar process to that described in example Z-2. 16 (40 mg, 0.088 mmol) and [(3/i)-3-aminobutyl](l-methylethyl)amine (78 mg, 0.60 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4/e,12a)-N-[(4-fluorophenyl)methyl]-4-methyM-(l-methylethyl)-6,8-dioxo-7-[(phenyl methyl)oxy]'l,2,3)4,6,8,12,12aoctahydropyi-ido[r,2l:4,5]pyrazino[l,2--3]pyrimidine-9-c arboxamide (26 mg, 56%). This material was hydrogenated in a second step as described in example Z"2 to give (4/?,12a/?)-Ar-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyll-(l-methylethyl)-6,8-dioxo -l,213,4,6,8,12,12a-octahydi-opyrido{l',2,-4-,5.]pyi-azino(l,2-a]pyi-imidine-9-cai'boxamide (21 mg, 90%) as an off-white solid. 'H NMR (400 MHz, CDCh) 8 1.01 (d, J= 5.6 Hz, 3H), 1.06 (d, J= 6.0 Hz, 3H), 1.31 (d, J= 6.8 Hz, 3H), 1.57 (m, 1H), 1.98 (m, 1H),
167

2.70-2.82 (m, 2H), 3.15 (m, 1H), 4.15-4.19 (m, 1H), 4.30 (m, 1H), 4.48 (s, 1H), 4.54-4.59 (m, 2H), 4,97 (m, 1H), 6.98 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.49 (s, 1H), 12.52 (s, 1H).
Example Z-31:
(46,,12a6)-Af-[(2,4-Difluorophenvl)methvll-7-hvdroxv-4-methvl-l-(2-methylpropvl)-6,8-dioxo-l,2.3.4,6,8,12.12a-octahvdi-opvrido[r.2':4.5]pvi-azino[l.2-]pvrimidine'9carboxa mide.

a) 1,1-Dimethylethyl [(.l.S)-2-cyano-l-methylethyl]carbamate. The nitrile was prepared in two steps using- a modified procedure as described in example Z-29. To a stirred solution of (2S)-2-({[(l, l.-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (8.40 g, 33.2 mmol) in DMSO (50 mL) and KCN (6.51 g, 100.0 mmol) cooled to 0 °C was added 18-crown-6 (9.05 g', 34.3 mmol). The solution was allowed to warm to room temperature and then heated to 70 °C for 1 hour. After cooling at room temperature, water was added and the mixture was extracted with Et20. The ethereal layers were washed with a brine solution, dried over Na'iSO-i, filtered and concentrated to give 1,1'dimethylethyl [(l6)-2-cyano-l-methylethyl]carbamate (5.37 g, 88%) as a pale yellow solid. 'H NMR (400 MHz, CDCla) 8 1.32 (d, J= 6.8 Hz, 3H), 1.44 (s, 9H), 2.52 (dd, /= 4.0, 16.4 Hz, 1H), 2.74 (m, Jl-l), 3.95 (m, 1H), 4.65 (br s, 1H).
168

b) [(35)'3-Aminobutyl](2-mefchy]propyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. 'H NMR (400 MHz, CDCh/CDaOD) 6 0,99 (m, 6H), 1.34 (m, 3H), 2.13-2.27 (m, 3H), 2.76 (m, 2H), 3.07 (m, 2H), 3.47 (m, 1H), 8.22 (m, 1 H), 8.83 (m, <1 H).
c)
(46'112a5)-/[(2,4-Difluorophenyl)methyl]-7-hydi-oxy-4-methyl-l-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[l',-2,:4,5]pyrazino[l,2-a]pyrimidine'9-carboxa mide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 nig, 0.17 mmol) and free based [(3S)-3_aminbbufcyl](2-methylpropyl)amine (107 mg, 0.74 mmol) were reacted in dichloromethane (2 raU with acetic acid to give (4.9,12a6)-Ar-[(2,4-difluorophenyl)methylJ-4-methy]-l-(2-metbylpropyl)-6,8-dioxo-7-[(p henylmethyl)oxy]-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5jpyrazinol.l,2-a]pyrimidi ne-9-carboxamide (76 rag, 76%) as a film. This material was hydrogenated in a second step as described in example Z"2 to give (4 dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[r,2,."415]pyrazino[l;2vi]pyrimidine-9-carboxa mide (39 mg, 80%) as an off-white solid. 'H NMR (400 MHz, CDCla) 8 0.76 (d, J- 6.4 Hz, 3H), 0.84 (d, J= 6.4 Hz, 3H), 1.32 (d, J- 7.2 Hz, 3H), 1.45-1.50 (m, 1H), 1.60-1.69 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.93 (in, 1H), 4.16-4.25 (m, 2H), 4,45 (s, lH), 4,57-4.68 (m, 2H), 4,96-5.01 (m, 1H), 6.75-6.82 (m, 2H),
369

7.32-7.38 (m, 1.H), 8.26 (s, 1H), 10.45 (s, 1H), 12.56 (s, 1H); ES+ MS: 475 (M+l).
Example Z-32:
(4612a6) r(Cvclopropvlmethvl)-Ar-[(2.4-difluorophenvl)methvlj-7-hvdroxv4-methvl-6 ,8-dioxo-1.2,3.4.6.8,12,12a-octahvdropvrido[l'.2':4,5lpvrazino[l,2-a]pvrimidine-9-cai"bo xamide.

a) l,l-.Dimethylethyl {(l5)'3-[(cyclopropylmethyl)amino]-l-rnethylpropyl}carbamate. The protected diamine was prepared using' a modified procedure as described in example Z-29. 1,1-dimethylethyl [(l6)'3_amino] methylpropyljcarbamate (0.293 g, 1.56 mmol), cyclopropane carboxa Idehyde (96 pL, 1.30 mmol), and sodium triacetoxyborohydride (0.439 g, 2.07 mmol) were stirred in a 1:1 mixture of anhydrous dichloroethane and tetrahydrofuran (10 m.L) at ambient temperature overnight. The reaction was quenched by the addition of saturated NaHCOs and then extracted with EtOAc. The combined extracts were washed with saturated NaHCOs, then a solution of brine, dried over Na2SO.i, filtered and concentrated. The residue was purified by flash chromatography (80:19:1. CHCh/MeOH/NH.iOH (37%) gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl {(l6)-3-l(cyclopropylmethyl)amino]-l-methylpropyl}carbamate (76 mg, 26%) as a clear oil. 'H NMR (400 MHz, CDCb) 6 0.09-0.13 (m, 2H), 0.44-0.49 (in, 2H), 0.92-0.95 (m, lB), 1.14 (d, J= 6.4 Hz, 3H), 1.43-1.70 (m, 12H), 2.38-2.50 (m, 2H), 2.62-2.73 (m, 2H),
170

3.74 (m, 1H), 4.88 (m, 1H).
b) [(36)-3-Aminobutyl](cyclopropylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. W NMR (400 MHz, CDCI:)/CD:sOD) 8 0.40 (m, 2H), 0.64 (m, 2H), 1.15 (m, 1H), 1.34 (m, 3H), 2.12-2.25 (m, 2H), 2.82 (m, 2H), 3.08 (m, 2H), 3.47 (m, 1H), 8.25 (br, < 1H), 9.04 (br, < 1H).
c)
(45',12a)-I-(Cyclopropylmethyl)-Ar-K2,4-difluorophenyl)methyl.]-7-hydroxy-4-methy]-6,8'dioxo-I,2,3,4,6,8,12,12a'Octahydropyridoll',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.106 mmol) and free based I(3j£>-3-aminobutyl](cyclopropylmethyl)amine (44 mg, 0.31 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(46',12aiS)-I-(cyclopropylmethyl)-jV-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-f(phenyl me thy Doxy]-1,2,3,4,6,8,12,12a-octahydropyrido[.I',2':4,5]pyrazino[l,2-#]pyrimidine-9-carboxamide (50 mg, 83%) as a film. This material was hydrogenated in a second step as described in example Z_2 to give
(4S, 12a6)-.I-(cyclopropylmethyl)-A/'-[(2,4-difluorophenyl)methyl]-7-hydroxy'4-meth3'I-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyridofI',2,:4,5]pyrazino[l,2-<3]pyrimidine-9-carboxamide (23 mg, 56%) as an off-white solid. »H NMR (400 MHz, CDCla) 5 0.11 (in, 2H), 0.56-0.59 (m, 2H), 0.77 (m, 1H), 1.34 (d, J= 7.2 Hz, 3.H), 1.46-1.50 (m, 1H), 2.04-2.13 (m, 1H), 2.30-2.34 (m, 1H), 2.46-2.51 (m, 1H), 2.90-2.96 (m, 1H), 3.16-3.19 (m, 1H),
171

4,21-4.30 (in, 2H), 4.51 (s, 1H), 4,58-4.67 (m, 2H), 5.00-5.05 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.37 (m, Hi), 8.28 (s, 1H), 10,46 (s, 1H), 12.55 (br, 1H); ES+ MS: 473 (M+I).
Example' Z-38:
(46,.12a6)-A-[(2,4-Difluorophenvi)methvl]-I-(2-furanvlmethvl)-7-hvdroxy-4-methvl-6,8•dioxo-I,2.3,4,6,8,12.12a-octahvdroBvrido[r.2':4,5)pvrazinofl.2-a]pvrimidine-9-carboxamide.

a) I.(36)-3-Aminobutyl](2-furanylmethyl)amiiie dihydrochloride was prepared in a similar manner as described in example Z"32. 'H NMR (400 MHz, CDCI3/CD3OD) 8 1.27 (d, J= 6.4 Hz, 3H), 1.96-2.05 (m, 1H), 2.14-2.19 (m, 1H), 3.00-3.04 (m, 2H), 3.38-3.39 (m, HI), 4.11-4,18 (m, 211), 6.34 (m, 1H), 6.59 (m, 1H), 7.40 (m, 1H), 8.18 (br, <1 H), 9.41 (br, < 1 H).
b)
(4iS',12aI-A':t(2,4-Difluorophenyl)methyl]-I-(2-furanylmethyl)-7-hydroxy-4-methyl-6>8-dioxo-I,2,3,4,6,8,12,12a-octahydropyrido[r)2':4,5]pyrazino[l,2-a]pyrimidine-9-car.boxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.076 mmol) and free based I(3iS)-3-aminobutyl](2-furanylmethyl)amine (70 mg, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
172

(45,12a-N-[(2,4-difluorophenyl)methyl]-I-(2-furanylmethyl)-4-methy]-6,8-dioxo-7-[(phenylmethyl)oxy]I,2,3,4,6,8I12,I2a-octahydropyridotri2'-'4,5]pyrazino[l,2-]pyrimidine-9-carboxamide (32 rag, 70%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give
(45',12a)-A':[(2,4-difluorophenyl)jnethyl]-I-(2-furanylinethyl)-7-hydroxy-4-methyl-6,8-dioxo-I)2,3,4,6,8,12,12a-octahydropyrido[l'12':4,5]pyrazino[l>2v7]pyrimidine-9-carboxamide (20 rag, 76%), as an off-white solid. 'H NMR (400 MHz, CDCla) 8 1.24 (d, J = 6.8 Hz, 3H), 1.451.49 (m, 1H), 2.04-2.13 (m, 1H), 2.77-2.82 (m, 1H), 2.94-3.01 (m, 1H), 3.65 (d, J= 15.6 Hz, 1H), 3.89 (d, J= 16.0 Hz, 1H), 4.27-4.31 (in. 1H), 4.39-4,41 (m, 1H), 4:49-4.53 (m, 1H), 4,58-4.66 (m, 1H), 4.98-5.03 (m, 1H), 6.24 (m, 1H), 6.36 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.39 (m, 1H), 7.40 (m, 1H), 8.26 (s, 1H), 10.47 (m, IH), 12.50 (br, 1H); ES" MS: 499 (M + I).
Example Z~34:
(46r.12a6)-7V-f(2.4-Difluorophenvl)methvl]-7-hvdroxv-4-methvl-6,8-dioxo-I-(I,3-thiazol-2-vlmethvl)-I,2.3.4.6,8,12,12a-octahvdropvridofr,2':4,5]pyrazino[l,2-a]pvrimidine-9-carboxamide.

a) f(3 in a similar manner as described in example Z-32. >H NME (400 MHz, CDCI3/CD3-OD) S 1.28 (d, J= 6.4 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 3.20 (m, 2H), 3.39 (m, 1H),
173

4.51-4.58 (m, 2H). 7.52 (d, 1H), 7.82 (d, 1H).
b)
(46',12a5)-N-f(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-I-(I,3-thilazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[l,,2':4,5jpyrazino[l,2-a]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (35 rag, 0.074 mmol) and free based [(3£)-3-amhiobiityl](I,3-tlnazol-2-ylmethyl)amine were reacted in dichloromcthane (2 mL) with acetic acid to give
(4-5',12a6)-A[(2,4-difluorophenyl)methyl]-4-methyl-6,8dioxo-7-[(pheaylmethyl)oxy]-I-(I,3-thia-/.ol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazinof.1,2-aJpyrimidine-9-carboxamide (36 mg, 80%) as a film. This material was debenzylated in a second step to in a manner similar to Z"26 to give
(46',12a6)-A-((2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-I-(].,3-thiazol-2-ylmethyl)-I,2,3,4,6,8,12,12a-octahydropyrido[l,,2,:4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide (18 mg, 60%) as an off-white solid. 'H NMR (400 MHz, CDCls) 6 1.30 (d, J= 7.2 Hz. 3H), 1.49-1.53 (m, 1H), 2.12-2.18 (m, 1H), 2.93-2.96 (m, 1H), 3.07-3.13 (m, 1H), 3.99-4,03 (m, 1H), 4.13-4.17 (m, 1H), 4,24-4,27 (m, IH), 4.57-4,61 (m, 3H), 5.03-5.06 (m, 1H), 6.75-6.82 (m, 2H), 7.26 (m, 1H), 7.31-7.37 (m, 2H), 7.76 (m, 1H), 7.94 (m, 1H), 10.40 (m, 1H), 12.48 (m, 1H); ES+ MS: 516 (M+I).

Example Z~35:
ra6YJ/n/ 174

4a,5,6a,7,II,I3,14a-decahvdro-2N-Dvridofr.2':4.5lpvrazinQ[I.2-][3,IIbenzoxazine-10-carboxamide

a)
rac6VJ3yc-(4a/i,,6a.,14a5)-N-K2,4-Difluoropheny])methylj-II,13-dioxo-I2[(phenylmethyDoxy] • 1,3,4,4a,5,6a,7,11,13,14adecahydro-2N'-pyrido[l'12,:4,5]pyrazino[l,2-a](3, ijbenzoxazine- 10 -carboxamide. i-ace./n/c-c/$-2-Hydroxyraethyl-I-cyclohexylarnine hydrochloride (24 mg, 0.186 minol) was dissolved in a dichloromethane solution containing a small amount of methanol (to dissolve) and excess MP Carbonate (Argonaut Technologies) was added, the mixture was stirred for 30 minutes, and the MPCarbonate was removed by filtration. The free amine solution was transferred to a microwave vessel containing 16a (29 mg, 0.0617 minol). One drop of glacial acetic acid was added and the solution was heated for 10 minutes at 140 "C. The resultant solution was absorbed on celite and the material was purified by silica gel chromatography (0'12% methanol/dichloromethane gradient elution) to yield the desired product as a white solid (18 mg, 53%). IH NMR (CDCla) 6 10.40 (m, 1 H), 8.35 (s, 1 H), 7.60 (m, 2 H), 7.34-7.26 (m, 4 H), 6.80 (m, 2 II), 5.35-5.23 (m, 2 H), 5.13 (m, 1 H), 4,77 (m, 1 H), 4,70 (m, 2 H), 4.22 (del, J= 13.2, 3.2 Hz, 1. H), 4.07 (dd, J = 13.2, 6.4, 1 H), 3.96 (m, 1 H), 3.76 (dd, ,/= 11.2, 4.4, 1 H), 2.22 (m, 1 H), 1.84 (m, 1 H), .1.74-1.40 (m, 6 H), 1.17 (m, 1 H)fES+ MS: 550 (M +1).
175

b)
raceyj;/c-(4ai?,6a7?,14a6)-A[(2,4-Difluoropheny])methylJ-12-hydroxy-11,13-dioxo-1,3,4,43,5,68,7,11,13,14a-decahydro-2Arpyridoll',2,:4,5]pyrazinofl,2-a][3,l]benzoxazine-10-carboxamide.
racemic (4a7?,6a.ff,14a5)-Ar-f(2,4-Difluorophenyl)methyl]-II,13-dioxo-12-[(phenylmethyl)oxy]-I,3J4)4a,5,6a,7,II,13,14a-decahydro-2Ar-pyrido[r,2':4,5]pyrazino[],2-a][3,l]benzoxazine-IOcarboxamide (13 mg, 0.0236 mmol) was dissolved in tetrahydrofuran and 10 w.t.% Pd/C (13 mg) was added. Hydrogen was passed through the solution several times and the mixture was stirred at 1 atm hydrogen for 18 hours until the reaction was determined complete by TLC (5% methanol/dichloromethane). The mixture was filtered through Celtite, eluting with methanol/chloroform and the filtrate was concentrated under reduced pressure and purified by HPLC to yield the title compound (7.3 mg, 73%) H NMR (CDCh) 6 12.45 (m, 1 H), 10.38 (s, 1 H), 8.30 (s, 1 H), 7.32 (m, 1 H), 6.83-6.76 (m, 2 H), 5.23 (m, 1 H), 4.75 (m, 1 H), 4,63 (m, 2 H), 4.26 (in, 1 H), 4.12-4.01 (m, 2 H), 3.83 (m, 1 H), 2.30 (m, 1 H), 1.91 (m, 1 H), 1.80 (m, 1 H), 1.67-1.40 (m, 5 H), 1.20 (m, 1 H); ES+ MS: 460 (M +1).
.Example Z-36:
i,aceyg-(4aAi,6a/14a)-Ar-[(4-Fluorophenvl)methvl]-12-hvdroxv-11,13-d ioxo-1.3.4,4a,5.6a,7.11.13.14a'decahydro-2N'-pvridofl'.2':4.5lpvrazinofl,2-fl1f3.l]benzoxazine'.10-carboxamide.
176

race/7j/c-(4a.II,6aR,14aS)-N-.[(4-Fluorophenyl)methy]]-II)13-dioxo-12-[(phenylmethyl)oxy]-l,3,4,4a,5,6a,7,II,13,14adecahydro-2H-pyridorr,2':4,5]pyrazino[l,2-aJ[v3,l]benzoxazine-10-carboxamide. In a manner similar to that described in example Z-35, from vv?ce7;j/2-HydroxymethyM'cyclo]iexylamine hydi'ochloride (50 rag, 0.303 mmol) and 16 (45 mg, 0.0995 mmol) was prepared
iVJce7;7yc-(4aR,6aR,14aS)-N-[(4-fluorophenyl)methyl]-II,13'dioxo-12'[(phenylmethyl)oxy]-I13,4,4a,5,6a,7,II,13J14a-decahydro-2H-pyrido[l,,2*:4,5jpyrazino[l,2-a][3,l]benzoxazine-10-carboxamide (48 mg, 91%) as a white solid. 'H NM.R (CDCI3) 5 10.42 (m, 1 l-l), 8.37 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 5 H), 6.98 (m, 2 H), 5.26-5.18 (m, 2 H), 5.07 (m, 3 H), 4.74 (m, 1 H), 4.62-4.5Km, 2 H), 4.20 (dd, J = 13.6, 4 Hz, 1 H), 4,04 (in, 1 H), 3.91 (m, 1 H), 3.71 (dd, J = 11.3, 4.8 Hz, 1 H), 2.18 (m, 1 H), 1.82 (m, 1 H), 1.73-1.63 (m, 2 H), 1.62-1.56 (m, 2 H), 1.48 (, 1 H), 1.38 (m, 1 H), 1.14 (m, 1 H); ES+ MS: 532 (M +1).
b)
racemJc-(4aIi,6a.R, 14a-N-[(4-Fluorophenyl)methylJ-I2"hydroxy-II,13-dioxo-1,3,4,4a,5,6a,7,II,13,14a-decahydro-2H-pyrido[r,2':4,5]pyrazino[l,2-a.][3,l]benzoxazine-10-carboxamide. In a manner similar to that described in example Z"37, from
i-ace77226'-(4aR,6aR,14aS)-N-[(4-fluorophenyl)methyl]-II,13-dioxo-12-[(phenylmethyl)ox
177

y]-l,3,4,4a,5,6aJ7,II,13l14adecahydro-2H-pyrido[l',2':4,5]pyrazino(l,2-a)[3,l]benzoxazine-10-carboxamide (37 mg, 0.06"96 mmol) and 10 w.t. % Pd/C (3 mg) was prepared the title compound (18 mg, 58%) as a white solid after purification by HPLC. JH NMR (CDCIs) 6 12.47 (s, 1 H), 10.39 (m, 1 H), 8.32 (s, 1 H), 7.30 (m, 2 H), 6.98 (m, 2 H). 5.22 (m, 1 H), 4.74 (m, 1 H), 4,58 (m, 2 H), 4,28 (dd, J- 1.3.2, 4 Hz, 1 H), 4.12-3.98 (m, 2 H), 3.81 (dd, J= 11.6, 4,8 Hz, 1 H), 2.29 (m, 1 H), 1.91-1.19 (m, 8 H); ES+ MS: 442 (M+!).
Example Z-'ST-
racemic -(36,,4a,6a,14a6ViV-f(2,4-.Difluorophei-ivl)methvll-12-hvdroxv-11.13-dioxo-3-phenvl-1.3.4.4a.5,6a.7,11.13,14a-decahvdro-2.:i3vrido[r.2':4.5]pvrazino[l,2-a1[3J.]benzoxazine-10-carboxamide.

a)
jvJceji'c-(3»S;4aI6a114a5)-At[(2,4-DifluorophenyDmethyl]-II,13-dioxo-3-phenyM2-[(phenylmethyl)oxy3-I,3,4,4a,5,6a,7,II,13,14a-decahydro-2Ar-pyrido[r,2':4,5]pyrazino[l,2-j3j[3,l]benzoxazine-10-carboxamide. In a manner similar to that described in example Z35, from rc7C(3vjj/c-[(l/£25,,55)-2-amino-5-phenylcyclohexyl]methanol hydrochloride (32 mg, 0.160 mmol) and 16a (30 mg, 0.064 mmol) was prepared

hydrochloride (32 mg, 0.100 mmol) and 10a (30 mg, 0.084 mmol) was prepared
iV9ce/;jic<36',4a/?,6ai?>14a6)-A'-[(2,4-difluorophenyl)methyl]-ll,13-dioxo-3-phenyM2-[(
phenylmethyl)oxy]-l,3,4,4a,5,6a,7,ll,13,14a-decahydro-2/7-pyrido[l',2':4,5]pyrazinoll,
178

2-a][3,.l]benzoxazine-10-carboxamide (35 mg, 88%) as a white solid. >H NMR (CDC13)
6 10.41 (m, 1 H), 8.38 (s, 1 H), 7.66 (in, 2 H), 7.40-7.26 (m, 6 H), 6.81 (in. 3 H),
5.32-5.25 (m, 2 H), 5.17 (m, 1 H), 4.89 (m, I H), 4.66-4.62 (m, 2 H), 4.26 (dd, J= 13.6,
4 Hz, 1 H), 4.13-4.04 (m, 2 H), 3.85 (dd, ,7=11.2, 4.4 Hz, 1 H), 2.56 (m, 1 H), 2.37 (m, 1
H), 2.03-1.64 (m, 6 H); ES" MS: 626 (M +l).
b)
i-aceyjjy phenyl-l,3,4,4a,5,6a,7,ll,13)14a-decahydro-2:pyrido[r,2,:4,5]pyrazino[l,2-d[3,l]ben
zoxazine- 10-carboxamide.
rce2ic-(36'",4ay?,6aie)14ai55-7V-[(2,4-Difluorophenyl)methyl]-ll,13-dioxo-3-phenyl-12-[(
pheiiylmethy])oxy]-l,3,4,4a>5,6a,7,ll,13,14a-decahydro-2/3r-pyiido[r,2':4,5]pyrazino[l1
2-a] [3, ljbenzoxazine- 10-carboxamide (27 mg, 0.0432 ramol) was suspended in
methanol, 10 w.t. % Pd/C (3 mg) was added and hydrogen was bubbled through the
system several times until the reaction was determined complete by TLC (5%
methanol/dichloromethane). The suspension was filtered through Celite eluting with
methanol/chloroform and the filtrate was concentrated under reduced pressure and
purified by HPLC to give the title compound (13 mg, 57%) as a white solid. 'H NMR
(CDCb) 6 12.40 (br s, 1 H), 10.37 (m, 1 H), 8.32 (s, 1 H), 7.37-7.28 (m, 3 H), 7.24-7.15
(m, 4 H), 6.79 (m, 2 H), 5.78 (br s, 1 H), 4.85 (m, 1 H), 4.62 (m, 2 H), 4.29 (m, 1 H),
4,16-4.09 (m, 2 H), 3.92 (dd, J= 11.6, 4.8 Hz, 1 I-l), 2.58 (m, 1 H), 2.46 (m, 1 H),
2.07-1.64 (ra, 7 H); ES+ MS: 536 (M +l).
179

Example Z-38:
Sodium
racgm/c-(4aS,6aS,14aS)-10-({f(2,4-difluorophenvl)methvi3amino}carbonvl)-6(2-methvl
propy])-.ll,13-dioxo-1.2,3,4,4a. 5,6.6a,7,11.13.14a-dodecahvdropvrido[l'.2':4,5]pyrazino[

a) 7-ace7J2ic-l,l'Diinethy]ethyl [(IS,2R)-2'(hydroxymethyl)cyclohexylJcarbamate.
y7CG/J7/c-[(l-/26',55)-2-Amino-5-phenylcyclohexyl]methanol hydrochloride (800 mg,
4.82 mraol) was dissolved in MeOH (40 ml) and bis(l,l"dimethylethyl) dicarbonate
(1.16 g, 5.30 mmol) and triethylamine (4 mL, 28.92 mmol) were added and the
mixture was stirred 18 hours at ambient temperature. The solvents were removed
under reduced pressure, ethyl acetate and aqueous saturated sodium bicarbonate
were added and the product was extracted with ethyl acetate. The combined
organics were dried over sodium sulfate and the solvents were removed under reduced
pressure. Purification by silica gel chromatography (9-'l hexanes'- ethyl acetate to
ethyl acetate gradient elution) gave IJ.-dimethylethyl
j,ace7J2/c--[(IS,2R)-2-(hyd.roxymethyl)cyclohexyl]carbamate (934 mg, 85%) as a white
solid. 'H NMR (CDCb) 5 4.87 (m, 1H), 4.03-3.95 (in. 2 H), 3.26 (m, .1 H), 3.15 (m, 1
H), 1.73-1.48 (m, 5 H), 1.38 (s, 9 H). 1.27-1.15 (m, 3 H), 0.887 (ra, 1 H).
b) vv3ce;j7ic-l,l-Dimethylethyl l(IS,2R)-2-FormylcyclohexyUcarbamatc. To a
180

solution of dimethylsulfoxide (0.2 mL, 2.88 mmoO in dichloromethane (3 raL) at -78 °C
was added oxalyl chloride (0.72 mL, 1.44 mmol) dropwise. The mixture was stirred
10 minutes and race-OT/e-l.l-dimethylethyl
((IS,2R)-2-(hydroxymethyl)cyclohexyl]carbamate (220 mg, 0.961 mmol) in
dichlormethane was added dropwise and stirred 10 minutes. Triethylamine (0.53 mL,
3.84 mmol) was added slowly and the reaction was stirred at -78 °C for one hour and
allowed to warm to ambient temperature. Water was added and product was
extracted with dichloromethane. The combined organics were washed with brine and
dried over sodium sulfate. Removal of solvents under reduced pressure afforded
jrace-m/c-l.l-dimethylethyl [(IS,2'R.)-2-formylcyclohexyl]carbamate (223 mg,
quantitative) as a yellow oil. 'H NMR (CDCLj) 5 9.61 (s, 1 H), 5.19 (in, 1 H), 3.88 (m,
1 H), 2.6.1 (m, 1 H), 1.85 (m, 1 H), 1.631.49 (m, 4 H), 1.371.16 (m, 12 H).
c) .race/n/c-l,l-dimethylethyl ((IS,2S)-2-{[(2-Methylpropyl)amino]methyl)
cyclohexyDcarbamate. race;;.?ic-l,l-Dimethylethyl
[(IS,2R)-2-formylcyclohexyl]carbamate (223 mg, 0.982 mmol) was dissolved in
dichloroethane and 2-methylpropyl)amine (0.15 mL, 1.47 mmol) and sodium
triacetoxyborohydride (290 mg, 1.37 mmol) were added and the reaction was stirred
at ambient temperature for 18 hours. Aqueous sodium bicarbonate was added and
the product was extracted with dichloromethane. The combined extracts were dried
over sodium sulfate and the solvents were removed under reduced pressure.
Purification by silica gel chromatography (dichloromethane to 1% ammonium
hydroxide 19% methanol 80% dichloromethane gradient elution) afforded
181

racenij'c-1,1 'dimethylethyl
((IS,2S)-2-{[(2-methylpropyl)amino]methyl}cyclohexyl)carbamate (112 mg, 40%) as a
clear colorless oil. 'H NMR (CDCLi) 6 6.06 (br s, 1 H), 3.76 (br s, 1 H), 2.63 (m, 1 H),
2.43-2.37 (m, 2 H), 2.25 (m. 1 H), 1.81 (m, 1 H), 1.71-1.59 (m, 3 H), 1.44-1.32 (m, 14 H),
1.27-1.19 (m, 2 H), 0.866 (m, 6 H).
d) raceauc-{IS,2S)-2-{[(2-Methylpropyl)amino]methyl}cyclohexanamine
hydrochloride.
In a manner similar to that describe in example Z_3, step e, from
racemic 1,1 -dimethylethyl ((IS,2S)-2-{[(2-methylpropyl)amino]methyl}
cyclohexyOcarbamate (112 nig, 0.394 mmol) was prepared
(].S,2S)-2-{((2-methylpropyl)amino]methyl}cyclohexanamine hydrochloride (130 rag, >
100%) as a white solid. 'H NMR (mcthanol-rfi/CDCls) 6 8.68-8.28 (ra, 1 H), 3.62 (br
s, 1 H), 3.26 (m, 1 H), 2.83-2.78 Cm, 3 H), 2.54 (br s, 1 H), 2.12 (m, 1 H), 1.82-1.66 (m,
3 H), 1.53-1.39 (in, 5 H), 0.96 (m, 6 H). 0.766 (m, 1 H).

e)
i-flcemyc-(4aS,6aS,14aS)-N-l(2,4-Difluoropheny0methyl]-6-(2-methylpropyl)ll
,13-dioxo-12-[(phenylmethyl)oxy]-.l,2,3,4,4a,5,6,6a)7lll,13,1.4a-dodecahydropyrido(l,,2'
4,5] pyrazino(l,2-a]quinazoline-10-carboxamide. In a manner similar to that
described in Z-35, from
i-ace;;]yc-(IS,2S)-2-{K2-methylprop}rl)amino]methyl}cyclohexanamine hydrochloride
(130 rag, 0.508 mmol) and 16a (55 rag, 0.117 mmol) was prepared
182

i'ace/j7/c-(4aS,6aS,14aS)-N-[(2)4-difluorophenyl)methylJ-6-(2-methylpiopyl)-ll,13diox
o-12-[(phenylmethyl)oxy]-l,2,3,4,4a,5,6,6a,7)ll,13>.l4a-dodecahydropyhdo[l',2,:4>5]
pyrazino[l,2-ajquinazoline-10-carboxamide (44 mg, 62%) with a 12-' 1 d.r. 'H NMR
(CDC13) 6 10.46 (m, 1H), 8.33 (s, 1 H), 7.59 (m, 2 H), 7.37-7.24 (m, 4 H), 6.79 (m, 2 H),
5.30-5.23 (m, 2 H), 4,75-4.56 (m, 3 H), 4,23-4,09 (m, 3 H), 2.69-2.66 (m, 2 H), 2.21-1.98
(m, 3 H), 1.80 (ra, 1 H), 1.71-1.33 (m, 6 H), 1.26-1.19 (m, 2 H), 0.810 (m, 3 H), 0.720 (m,
3 H); ES+ MS: 605 (M +1).
f)
iv?cey;ji'c-(4aS,6aS,]4awS)-N-[(2,4-Difluorophenyl)inethyl]-12-hydroxy-6-(2-meth
ylpropyl)-ll,13-dioxo-l,2,3,4,4a,5,6,6a,7,ll, 13,14a-dodecahydropyrido[.l',2':4,5Jpyrazin
o[l,2-a]quinazoline-10-carboxamide. In a manner similar to that described in
example Z'37, from
i-c-3ce;7j/c-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl).methyl]-6-(2-methylpropyl)-ll,13-diox
0-12-t(phenylmethy])oxy]-l,2,3,4,4a,5,6,63,7,11,13,14adodecahydropyrido[r,2':4J5]
pyraziiio[l,2-a]quinazoline-10-carboxamide (39 mg, 0.064 mmol) and .10 w.t. % Pd/C (7
mg) was prepared
i-ace7;;yc-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-6-(2-methylpi;opyl)
-ll.ia-dioxo-l.Sa.e.ea.ll.IS.Ha-dodecahydropyridofr'.Sjpyrazinoll-ajq
uinazoline-10-carboxamidc (36 mg, > 100%) as a tan solid. >H NMR (CDCL-0 6 12.60
(br s, 1 H), 10.43 (br s, 1 H), 8.25 (s, 1 H), 7.35 (m, 1 H), 6.78 (m, 2 H), 4.77 (m, 1 H),
4.63 (111, 2 H), 4.49 (br s, 1 li), 4.30-4.13 (m, 2 H), 3.63-3.40 (m, 2 H), 2.88-2.71 (in, 2
H), 2.32-2.21 (m, 2 H), 2.05 (m, 1 H), 1.88-1.11 (m, 7 H), 0.830 (m, 3 H), 0.760 (m, 3
183

H); AP+MS: 515 (M+l).
g) Sodium
i-c propyl)-ll,13-dioxo-l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido(r,2':4,5]pyrazinof
l,2-a]quinazoliii-12olate. In a manner similar to that described in example Zl,
from
i-acei7b-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)
-ll,13-dioxo-l,2,3,4,4a,5,6,6a,7,ll, 13,14a-dodecahydropyrido[r,2':4,5]pyrazino[l ,2a]q
uinazoline-10-cax-boxamide (37 mg, 0.071 mmol) and 1 N sodium hydroxide (0.07 mL)
the title compound was prepared as a yellow solid (26 mg, 68 %). 'H NMR
(DMSO-rffi) 5 10.73 (m, 1 H), 7.94 (s, 1 H), 7.32 (m, 1 ll), 7.19 (m, 1 H), 7.00 (m, 1 H),
4,59-4.41 (m, 3 H), 4,28 (m, 2 H), 4.14 (br s, 1 H), 2.632.60 (m, 2 H), 1.981.61 (m, 5
H), 1.48-1.36 (m, 4 H), 0.997 (m, 3 H), 0.760 (m, 3 H), 0.660 (m, 2 H); AP- MS: 515
(M+l of free acid).
Example Z'39<'
(6aR.7aS,llaS)-N-K2,4-DifluoroDhenvl)methvll-l-hvdroxv-2.13-dioxo-2,6a.7,7a.8.9.10.
ll,lla,13-decahvdro-6H-pyrido[r.2':4,5]pvra2ino[l,2-aJben7,imidazole-3-carboxamide
& Example Z-4Q:
(6aS.7aS.llaS)-N-K2,4-Difluorophenvl)methvn-.l-hvdroxy-2,13-dioxo-2,6a,7,7a.8.9.10.
ll.ll.a,13-decahvdro-6H-pvridorr,2'-'4,5]pvrazinofl,2-albenzimidazole-3-carboxamide.
184

a)
(6aR,7aS,llaS)-N-[(2J4-Diflnorophenyl)methyl]-2,13-dioxo-l-[(phenylmethyl)o
-xy]-2,6a,7,7a,8,9,10,ll,lla,13decahydro-6H-pyrido fl'.2':4,5] pyrazino[l,2-a)
benzimidazole-3-carboxamide and
(6aS,7aS1.llaS)-N-((2,4-difluorophenyl)methyl]-2,13-dioxo-l-((phenylmethyl)oxy]-2,6a,
7,7a,8,9,10,ll,lla,13-decahydro-6H-pyrido[l',2'-'4,5]pyrazino[l,2-a]benzimidazoJe-3-ca
rboxamide. In a manner similar to that described in example Z-2, from
[(IS,2S)-2-aminocyclohexyl] amine (122 mg, 1..07 mmol) and 16a (200 mg, 0.426 mmoi)
was prepared
(6aR,7aS,]3aS)-N-l(2,4-difluorophen.yl)methyl)-2,13-dioxol-((phenylmethyl)oxyJ-2,6a,
Va.S.O.lOJl.lla.ISdecahydro-fiH-pyrido fl',2':4,5) pyi.-azinoCl.2-a]
ben7.imidazole-3carboxamide (58 mg) and
(6aS,7aS,llaS)-N-[(2,4-difhiorophenyl)methyl]-21i:3dioxol-[(phenylmethyl)oxy]-2,6a.
7,7a,8,9,10,ll,n.a,13-decahydro-6li-pyrido|.l',2':4,5]pyi-azino[l,2-albeiizimidazoJe-3-ca
rboxamide (10.6 mg-) after separation of the diastereomers using silica gel
chromatography (0-12% methanol/dichloromethane).
(6aR,7aS,llaS)-N-[(2,4-difliiorophenyl)methyl]-2,13-dioxo-l-{(phenyhnethyl)oxy]-2,6a,
7,7a,8,9,10,ll,lla,13-decahydro-6Hpyrido (l',2':4,5] pyrazino[l,2-a]
benzimidazole-3-carboxamide (major): 'H NMR (CDCln) 6 10.40 (in, .1 H), 8.33 (s, J
H), 7.57 (m, 2 H), 7.40-7.25 (m, 4 H), 6.81 (ni, 2 H), 5.32 (d, J= 10 Hz, .1 H), 5.13 (d, 185

= 10 Hz, 1 H). 4.64-4.58 (m, 3 H), 4.21 (dd, /= 12,4, 3.2 Hz, 1 H), 3.79 (in, 1 H), 3.04
(m, 1 H), 2.73 (m, 1 H), 2.53 (m, 1 H), 2.01-1.79 (m, 4 H), 1.36-1.24 (m, 4 H); ES< MS:
535 (M +.1).
(6aS,7aS,llaS)-N-[(2,4-difluorophenyl)methy]]-2,13-dioxo-l-[{phenylmethyl)oxy]-2,6a,
7,7a,8,9,10,ll,lla,13-decahydro-6H-pyridolr,2':4,5jpyrazino[l,2-a]benzimidazole-3-ca
rboxamide (minor diastereomer): 'H NMR (CDCla) 6 10.33 (m, 1 H), 8.28 (s, 1 H),
7.61 (in, 2 H), 7.39-7.28 (m, 3 H), 6.79 (m, 2 H), 5.29 (d, J- 9.6 Hz, 1 H), 5.05 (d, J =
9.6 Hz, 1 H), 4.84 (m, 1 H), 4,60 (m, 2 H), 3.90-3.84 (m, 2 H), 3.07 (m, 1 H), 2.75 (m, 1
H), 2.49 (m, 1 H), 2.07 (m, 1 H), 1.90-1.51 (m, 4 H), 1.33-1.19 (in. 4 H); MS data

matches that of its diastereomer.
b) (For example Z-39).
(6aR,7aS,IIaS)-N-[(2,4-Difluorophenyl)methyl]-l-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,
II,IIa,13-decahydro-6H-pyrido[r,2':4,5]pyrazinol],2-a]benzimidazole-3-carboxamide.
In a manner similar to that described in example Z-37, from the minor diastereomer
prepared in step a
(6aS,7aS,IIaS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-l-t(phenylmethyl)oxy]-2,6a,
7>7a,8,9,10,II,IIa,13-decahydro-6H-pyrido[r,2':4,5]pyrazino[l,2-a]benzimidazole-3-ca
rboxamide (7 mg, 0.0131 mmol) and 10 w.t. % Pd/C (catalytic amount) was prepared
(6aR,7aS,IIaS)-N-l(2,4-difluorophenyl)methyl]-l-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,
1.1,11a, 13-decahydro-6H-pyrido[r,2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide
(2.8 mg, 48%) after purification by HPLC. H NMR (CDCl3) 5 12.15 (br s, 1 H),
10.42 (br s, 1 H), 8.31 (s, 1 H), 7.36 (m, 1 H), 6.80 (m, 2 H), 5.01 (m, 1 H), 4.63 (m, 2
186

H). 4.16 (m, 1 H), 3.96 (m, 1H), 3.06-2.93 (m, 2 H), 2.61 (m, 1 H), 2.18 (m, 1 H), 1.93
(m, I H), 1.60-1.13 (m, 4 H), 0.893-0.840 (m, 2 H); ES+ MS: 445 (M +1).
c) (For example Z-40).
(6aS,7aS,IIaS)-N-l(2,4-Di£luorophenyl)methy]]-l-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,101
II,I.la,13-decahydro-6H-pyrido[r,2'4,53pyi-azino[l,2-a]benzimidazole-3-carboxaii]ide.
In a manner similar to that described in example Z-37, from the major diastereomer
(30 mg, 0.0561 mmol) prepared in step a and 10 w.t. % Pd/C (catalytic amount),
(6aS,7aS>IIaS)-N-K2,4-Difluorophenyl)methyl]-l-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,
II,I.la,13-decahydi-o-6H-pyrido[r,2':4,5]pyrazino(l,2-a]benzimidazole-3-carboxamide
was prepared as a white solid (15 mg, 60%) after purification by HPLC. 'H NMR
(methanol-rfi/CDCla) 5 10.41 (m, 1 H), 8.25 (s, 1 H), 7.30 (m, 1 H), 6.77 (m, 2 H), 4,77
(m, 1 H), 4.67 (m, 2 H), 4.45 (m, 1 H), 3.91 (m, 1 H), 3.12 (m. 1 H), 2.67 (in, 1 H), 2.12
(m, 1 H), 1,87-1.84 (m, 2 H), 1.47-1.33 (m, 4 H); ES+ MS: 445 (M +1).
Example Z-41:
(5aS.14aS)-N-|X2,4-Difluorophenyl)methyl]-11 hydroxy 10,12-dioxo-1.2,3.4,5a.6.10.12.
14,14a'decahydropvrido[l,2-alpyridofr.2':3,4limidazofl,2-d]pyrazine-9-carboxamide,

a)
(5aS,14aS)-N-((2,4-Diflnorophenyl)methyl]-10,12-dioxo-ll-[(phenylmethyl)oxy]-1,2,3,4 •
187

,5a,6,10,12, M.Ha-decahydropyridotl-aJpyridotl'JimidazoU-dlpyrazine-car
boxamide. In a manner similar to that described in example Z-18, from 16a (50 mg,
0.108 mmol) and ((2S)-2-piperidinylmethyl]amine hydrochloride (50 mg, 0.269 mmol,
made in a similar manner as described in example Z-18) was prepared
(5aS,14aS)-N-[(2,4-difluorophenyl)methyl]-10,1.2-dioxo-ll-[(phenylmethyl)oxy]-1,2,3,4,
5a,6,10,12,14,14a-decahydropyridoll,2-a]pyridolr,2':3,4]imidazo[l,2-d]pyrazine-9-car
boxamide (40 mg, 78 %). H NMR (CDCls) 5 10.43 (in, 1 H), 8.38 (s, 1 H), 7.59 (m, 2
H), 7.59-7.25 (m, 4 H), 6.81 (m, 2 H), 5.38 (d, J= 10 Hz. 1 H), 5.19 (d, /= 10 Hz, 1 H),
4.65-4.62 (m, 2 H), 4.20 (dd, J- 12, 2.8 Hz, 1 H), 4,00 (dd, J= 12.4, 2.8 Hz, 1 H), 3.85
(m, 1 H), 3.74 (m, 1 H), 3.27 (m, 1 H), 2.99 (m, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 li),
1.94-1.87 (m, 2 H), 1.77-1.58 (m, 2 H), 1.39-1.24 (m, 2 H); ES+ MS: 535 (M +1).
b>
(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-ll-hydroxy-10,12-dioxo-l,2,3,4,5a,6,10,12,
14)14a-decahydropyrido[l,2-a]pyrido[l,,2';3,4]imidazo[l,2-d]pyrazine-9-carboxamide.
Tn a manner similar to that described in example Z-37, from
(5aS,14aS)-N-f(2,4-difluorophenyl)methyl]-10112-dioxo-ll-[(phenylmethyl)oxy]-1,2,3,4,
5a,6,10,12,14,3 4a-decahydropyrido[l,2-a]pyrido(r,2':3,4]imidazo[l,2-dJpyi-azine-9-car
boxamide (18 mg, 0.0337 mmol) and 10 w.t.% Pd/C (catalytic amount) was prepared
the title compound as a white solid (13 mg, 87%) after purification by HPLC, 'H
NMR (CDCls) 6 11.71 (br s, 1 H), 10.36 (br s, 1 H), 8.31 (s, 1 H), 7.34 (m, 1 H), 6.78
(m, 2 H), 4,64-4,57 (m, 2 li), 4,28 (m, 1 H), 4.12 (ra, 1 H), 3.92-3.89 (in, 2 H), 3.22 (m, 1
H), 3.04 (m, 1 H), 2.49 (m, 1 H), 2.28 (m, 1 H), 1.97-1.89 (m, 2 H), 1.78 (m, 1 H),
188

1.66-1.60 (m, 2 H), 1.43-1.36 .Example Z-42:
(4aR..14aR)-N-K2.4-DifluoroDhonvl)methvl]-9-hvdroxv8,10-dioxo-2,3.4.4a.5.6.8.10.14,
14a-decahvdro-lH-pvridofl.2-c]pvi'idolr.2':4.5]pvra2inori,2-a1pvrimidine-ll-carboxam
ide.

a) Phenylmethyl (2R)-2-(hydroxymethyl)-l'piperidinecarboxylate. In a manner
similar - to that devscribed in example Z3a, from
(2R)-.l-{|(pheny]methyl)oxy]carbony]}-2-piperidinecarboxylic acid (4.93 g, 18.75 nunol)
was prepared phenylmethyl (2R)"2-(hydroxymethyl)-].-piperidinecarboxylate (2.24 g,
48%) as an oil that solidified upon standing to a white solid.]H NMR (CDCh) 6
7.36-7.26 (in, 5 H), 5.18-5.10 (m, 2 H), 4.37 (m, 1 H), 4.03 (m, 1 H), 3.84 (, m, 1 H),
3.63 (m, 1 H), 2.96 (br s, 1 H), 1.71-1.42 (m, 6 H).
b) Phenylmethyl (2R)-2-(cyanomethyl)-l-piperidinecarboxylate. In a manner
similar to that described in example Z"3b, from phenylmethyl
(2R)-2-(hydroxymethyl)-l-piperidinecarboxylate (l.09g, 4.38 mmol) was prepared
phenylmethyl (2R)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)- 3 -piperidinecarboxylate
(l,05g, 59% impure with uncharacterized byproduct) as a clear colorless oil after-
purification using silica gel chromatography (10-100% ethyl acetate-hexanes). It is
189

necessary to use this material in the next step as soon as possible or yields
deteriorate dramatically. In a manner similar to that described in example Z-3c,
from phenylmethyl
(2R)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-l-piperidinecarboxylate 0.05 g, 2.61
mmol) and sodium cyanide (383 mg, 7.82 mmol) was prepared phenylmethyl
(2R)-2-(cyanomethyl)-l-piperidinecarboxylate (171 mg, 25 %) as a yellow oil. lti

NMR (CDCla) 5 7.35-7.29 (m, 5 H), 5.13 (s, 2 H), 4.65 (m, 1 H), 4.10 (m, 1 H), 2.96 (m, 1 H), 2.60 (m, 2 H), 1.82-1.67 (m, 4 H), 1.54-1.39 (m, 2 H).
d) Phenylmethyl (2R)-2-(2-aminoethyl)-l-piperidinecarboxylate. In a manner similar to that described in example Z-3d, from phenylmethyl (2R)-2-(cyanomethyl)-l-piperidinecarboxylate (171 mg, 0.663 mmol) was prepared phenylmethyl (2R)-2-(2-aminoethyl)-l-piperidinecarboxylate (1.19 mg, 68%) as a clear colorless residue. >H NMR (CDCla) S 7.32-7.25 (m, 5 H), 5.08 (m, 2 H), 4.39 (br s, 1 H), 4.01 (br s, 1 H), 2.78 (m, 1 H), 2.60-2.56 (m, 2 H), 1.95-1.86 (m, 3 H), 1.63-1.35 (m, 6 H).
e) {2-[(2R)-2-Piperidinyl]ethyl}amine. Phenylmethyl (2R)-2-(2-aminoethyl)-l-piperidinecarboxylate (119 mg, 0.454 mmol) was dissolved in methanol and 10 w.t.% Pd/C (120 mg) was added. Hydrogen was bubbled through the solution for 15 minutes and the reaction was stirred under]. atm hydrogen for 18 hours until determined complete by TLC (1% ammonium hydroxide 19% methanol 80% dichloromethane). The suspension was filtered through Celite eluting with
190

methanol and the filtrate was carefully concentrated under reduce pressure to yield a clear colorless liquid (58 rag, quantitative). 'H NMR (CDCb) 5 2.99 (m, 1 H), 2.71-2.66 (m, 2 H), 2.57-2.48 (m, 2 H), 1.72 (m, 1 H), 1.61-1.52 (m, 2 H), .1.48-1.42 (m, 2 H), 1.35-1.25 (m, 2 H), 1.05 (m, 1 H).
f)
(4aR,14aR,)-N-[(2,4-Difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-2,3,4,4,5,6,8,10,14,14a-decah.ydro-IH-pyrido[l,2-c]pyrido[l',2':4,5]pyrazino[lr2-a]pyrimidine-11-carboxamide. In a manner similar to that described in example Z-35, from 16a (50 mg, 0.106 mmol) and {2-[(2R)-2-piperidinyl]ethyl}amine (58 mg, 0.454 rainol) was prepared
(4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-Kphenylmethyl)oxy]-2,3,4,4a,5,6,8,10,14,14a-deca hydro-IH-pyrido[1,2-cjpyridoll', 2':4,5]pyrazino[l,2-a]pyrimidine-l 1-carboxamide (47 mg, 81%). 'H NMR (CDCls) 6 10.50 (br s, 1 H), 8.33 (s, 1 H), 7.60 (s, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.29-5.22 (m, 2 H), 4.66-4.56 (m, 3 H), 4.30 (m, 1 H), 4,19 (m, 1 H), 3.78 (br s, 1 H), 2.86-2.80 (m, 2 H), 2.18 (br s, 1 H), 1.94 (m, 1 H), 1.68-1.36 (m, 6 H), 1.23 (br s, 2 H); ES+ MS: 549 (M +l).
g)
(4aR,14aR)-N-((2,4-Difluorophenyl)methyl]-9-hydroxy8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-IH-pyrido[.I,2-c)pyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-H-carboxamide. In a manner similar to that described in example Z-37, from
(4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylme(.hy])oxy3-2,3,4,4a,
191

5,6,8,10l141Ha-decahydro-IH.-pyri-do[l,2'c]pyrido[l'l2,:415]pyra2ino[l,2-a]pyi'imidine-l 1-carboxamide (47 mg, 0.0857 ramol) and a catalytic amount of 10 w.t.% Pd/C was prepared the title compound as a white solid (19 mg, 54%) after purification by HPLC. iH NMR (CDC13) 6 10.49 (m, 1 H), 8.29 (s, 1 H), 7.34 (m. 1 H), 6.79 (m, 2 H), 4.67-4.56 (m, 3 H), 4.41 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1 H), 2.94-2.87 (m, 2 H), 2.28 (br s, 1 H), 2.01 (m, 1 H), 1.68-1.54 (m, 4 H), 1.44 (m, 1 H), 1.29-1.23 (m, 3 H), 0.850 (m, 1 H); ES+ MS-' 459 (M +1).
Example Z'43
(4/?.12a/?)-Ar-f(2.4-Difluorophenvl)methvll-7-hvdroxv-4-methvl-l-(3-methvlbutvl)-6.8-dioxo-1.2.3,4.6.8.12.12a-octahvdi-ODvrido[r,2'v4,5lpvrazino[l,2-a|pyrimidine-9 carboxamide.

a) [(3)-3"Ainobutyl](3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. 'H NMR (400 MHz, CDCI3/CD3OD) 6 0.87 (d, /= 5.2 Hz, 6H), 1.32 (m, 3H), 1.61 (m, 3H), 2,10-2.20 (m, 2H), 2.90-3.04 (m, 4l-l), 3.45 (m, IH), 8.23 (br, < I H), 8.96 (br, < 1 H)._
b)
(47?, 12a7?)-N-[(2,4-Dfluoropbenyl)methyl3-7-hydroxy4-methyl-l-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[l',2':4,5]pyrazino[l,2-]pyrimidine-9-carboxam
192

ide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.085 mmol) and free [(37Z)-3-aminobutyl](3-methylbutyl)amine (46 mg, 0.35 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(412a/0-A[(2,4-difluorophenyl)methyn-4-methyl-l-(3-methylbiityl)-618-dioxo-7-[(phenylmethyl)oxy]-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9'carboxamide (44 mg, 90%) as a film. This material was hydrogenated in a second step as described in example Z'2 to give
(4i?,12a-iV:[(2,4-difluorophenyl)methyl]-7-hydroxy4-methyl-].-(3-methylbutyl)-6,8-dioxo-].,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide (11 mg, 30%) as an off-white solid. >H NMR (400 MHz, CDCb) 8 0.84 (d, J= 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 1.24-1.36 (m, 6H), 1.47-1.53 (m, 2H), 2.02-2.11 (m, 1H), 2.36-2.43 (m, 1H), 2.54-2.61 (m, IH), 2.77-2.92 (m, 2H), 4.16-4.26 (m, 2H), 4,44 (m, 1H), 4.62-4,64 (m, 2H). 4.95-C.02 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37 (m, 1.H), 8.27 (s, 1H), 10.43 (m, 1H), 12.54 (s, 1H); ES' MS: 489 (M+l).
Example Z-44:
(46',12a6)-W-f(2,4-Difluorophenvl)methv]1-7-hvdroxv-4-methvl-l-(l-methvlethvl)-6.8-dioxo-1.2.3,4.6,8.12.12a-octahvdropvridofl',2':4.5lpyrazino[l,2-fl]pyrimidine-9-carboxamide.

193

a) [(3*S)-3-Aminobutyl](l-methylethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. 'H NMR (400 MHz, CDCI3/CD3OD) 5

1.20-1.25 (in, 9H), 1.93-2.02 (m, 2H), 2.92 (m, 2H), 3.20-3.29 (m, 2H), 8.04 (br, < 1 H), 8.64 (br, < 1 H).
b)
(45,,12a6)-A[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyM-(l-methylethyl)-6,8-di oxo-l,2,314,6)8,12)12a-octahydropyrido[l',2':4,5]pyrazino[l,2-]pyrimidine-9-carboxain

ide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(35)-3-aminobutyl](rmethylethyl)amine (55 mg-, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(46,,12a6)-Ar-[(2,4-difluorophenyl)methyl]-4-methyl-l-(lmethylethyl)-6,8-dioxo-7-((phe nylmethyl)oxy)-l,213,4,6,8,12,12a-octahydropyrido[r,2':4!5]pyrazino[l,2-]pyrimidine-9-carboxamicle (40 mg, 57%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give
(45',12a6)-yV-[(2,4-difluorophenyOmethyl]-7-hydroxy-4-methyl-l-(l-methylethyO-6,8-di oxo- l,2>3,4,6,8l12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxam ide (17 mg, 50%) as an off-white solid. 'H NMR (400 MHz, CDCh) 8 1.02 (d, /= 6.4 Hz, 3.H), 1.07 (d, J= 6.4 Hz, 3H), 1.33 (d, J= 7.2 Hz, 3H). 1.55-1.58 (m, 1H), 1.94-2.03 (m, 1H), 2.70-2.77 (m, 1H), 2.81-2.86 (m. 1H), 3.11-3.18 (m, 1H), 4.17 (dd, /= 3.0, 13.8 Hz, 1H), 4.32 (dd, J= 3.2, 14.0 Hz, 1H), 4.48 (m, 1H), 4.59-4.69 (m, 2H), 4,97-5.00 (m, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, Hi), 10.50 (m, 1H), 12.55 (s, 1H);
194

ES+ MS: 461 (M+l).
Example Z-45:
(46'.12a6)-y-|(2.4-Difluorophenvl)methvll-7-hvdroxv-4-methvM-(3-methvlbutvl)-6.8-d ioxo-1.2,3,4,6,8J2,.12a-octahydropyridotl\2M,5lpyrayJno[l,2-alpyrimidme-9-carboxa mide.

a) [(3iS)-3-AminobutylJ(3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. 'H NMR (400 MHz, CDCl3/CD3OD) 8 0.86 (d, 2.87-2.99 (m, 4H), 3.38 (m, 1H), 8.15 (br, < 1 H), 8.87 (br, <] H).
b)
(45,,12a-N-[(2)4-Difluorophenyl)methyl]-7hydroxy-4-methyM-(3-methylbutyl)-6,8-d ioxo-l,2,314,6,8,12,12a-octahydropyrido(r,2,:4)5]pyra7Jino[l,2-]pyrimidine-9-carboxa mide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (0.100 g, 0.21 mmol) and free based [(3i5)-3-aminobutyl](3-mcthylbut.yl)amiiie (0.104 g, 0.66 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(45,)12a6)-Ar-((2,4-difluorophenyl)methyl]-4-methyM-(3-methylbutyl)-6,8-dioxo-7-l(ph enylmethyl)oxy]-l,2,3,4,6,8,12,12a-octahydropyrido[l',2':4,5]pyrazino[l,2-]pyrimidine
195

-9'carboxamide (88 mg, 72%) as a film. This materia] was hydrogenated in a second step as described in example Z'2 to give
(46;i2a-jV-[(2,4-difluorophenyl)methyl]-7-hydroxy4-methyM-(3-methylbutyl)-6,8-di oxo-l.S.e.S..a-octahydropyridofr'-.SJpyrazinotl-aJpyrimidine-O-carboxam ide (65 mg, 74%). >H NMR (400 MHz, CDCh) 6 0.84 (d, J= 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 1.24-1.37 (m, 5H). 1.45-1.53 (m, 2H), 2.02-2.11 (m, 1H), 2,37-2,44 (m, 1H), 2.56-2.63 (m, 1H), 2.80-2.92 (m, 2H), 4.22-4,29 (in, 2H), 4.45 (s, 1H), 4.62-4.63 (m, 2H), 4,97-5.00 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.37 (m, 1H), 8.37 (s, 1H), 10.48 (m, 1H), 12.53 (br, 1H); ES' MS: 489 (M+l).
Example Z-46:
(46',12a5)-N-((2,4-Difluorophenvl)me.thyll-7-hydroxy-4-methvl-6.8-dioxo-,l-(3-Dvridinvl methyl)-1,2,3.4,6.8,12,12a-octahvdroBvridofl'.2':4,5.1pyrazino[1,2-alpyrimidine-9 cai-bo xamide.

a) 1,1-Dimethylethyl {(IAS)-l-methyl-3-[(3-pyridinyhnethyl)amino]propyl}carbamate. The protected diamine was prepared using a modified procedure as described in example Z-32. A solution of 1,1-dimethylethyl [Q.j5!)-3-amino-l-methylpropyl]carbamate (0.296 g, 1.6 mmol) and 3-pyridinecarboxaldehyde (.120 u'L, 1.3 mmol) in a 11 mixture of anhydrous dichloroethane and tetrahydrofuran (10 mL) was treated with acetic acid (374 uL, 6.6

196

mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 2 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give
1,1-dime thylethyl {(l-l-methyl-S-RS-pyridinylmethyDaminolpropylJcarbamate (0.245 g, 66%) as a clear oil. 'H NMR (400 MHz, CDCla) 6 1.12 (d, /= 6.4 Hz, 3H), 1.42 (s, 9H), 1.46-1.54 (m, Hi), 1.68 (m, 1H), 2.61-2.75 (m, 2H), 3,73- 3.80 (m, 3H), 4.86 (m, 1H), 7.22-7.24 (m, 1H), 7.68 (d, b) [(3iS)-3-AmmobutylJ(3-pyridinylmethyl)amine dihydrochloride was prepared in a
similar manner as described in example Z~29.
c)
(46", 12a6)-Ar-[(2,4-Difluorophenyl)methyl]-7-hyd roxy'4-methyr6,8"dioxo- l.-(3-pyridinyl methyl)- l,2,3,4,6,8,12,12a-octahydropyrido[l',2':4,5]pyrazino[l,2-]pyrimidine-9carbo xamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(36)-3-aminobutyU(3-pyridinylmethyl)amine (83 mg, 0.47 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(45,,12a-5)-Ar-K2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-l(phenylmethyl)oxyJ-l-(3-pyridiiiylmethyl)-l,2,3,4,6,8,12,12a-octahydropyrido(r,2':4,5]pyrazinofl,2-i3)pyrimi dine-9-carboxamide (72 mg, 95%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give
(46',12a5)-A-[(2,4-difluorophenyl)methyl]-7-hyd roxy 4-methyl-6,8-dioxo- l-(3-pyridinyl
197

197

methyl)-1,2,3,4,6,8,.a-octahydropyridoll'.SjpyrazinoU-tfJpyrirnidine-carbo xamide (34 mg, 56%) as an off-white solid. >H NMR (400 MHz, CDCla) 6 1.37 (d, J = 6.8 Hz, 3H), 1.43-1.47 (m, 1H), 2.12 (m, 1H), 2.60-2.92 (m, 2H), 3.53 (d, /= 14.0 Hz, 1H). 3.82 (d, J- 14,4 Hz, 1H), 4.23-4.31 (ra, 2H), 4.55-4.64 (m, 3H), 5.06-5.11 (m, 1H), 6.75-6.82 (m, 2H), 7.20-7.23 (m, 1H), 7.31-7.36 (m, 1H), 7.50 (m, 1H), 7.92 (s, 1H), 8.48 (s, 1H), 10.39 (m, 1H), 12.5 (br, 1H); ES< MS: 510 (M+l).
Example Z-47:
{AS, 12a6)-l-Cvclopropvl-N-f(2,4-difluorophenvl)methvi]-7-hvdroxv4-methvl-6,8-dioxo-1.2.3,4,6,8.12. 12a-octahvdropvrido[r,2'-'4.5lpvrazinof 1,2-alpyrimidine-9-carboxa mid e.

a) 1,1-Dimethylethyl [(l6)-l'methyl-3'oxopropyl]carbamate. To a stirred solution of 1,1-dimethylethyl [(165-2-cyano-l-methylethyllcarbamate (0.656 g, 3.56 mmol) in anhydrous ether cooled to -40 °C was added dropwise a 1.0 M solution of diisobutylaluminum hydride in hexanes (14.2 mL, 14,2 mmol) over 20 minutes. Stirring was continued at this temperature for an additional 20 minutes. The yellow solution was quenched with Rochelle's salt and the resultant stirred at room temperature for .1. hour. The solids were filtered off through celite and rinsed with EtOAc. The organics were washed with brine, concentrated, and flash chromatographed (10-100% EtOAc/hexanes) to give 1,1-dimethylethyl [(l6)-l-methyl-3-oxopropyl]carbamate (0.193 g, 30 %) as a clear oil. 'H NMR (400
198

MHz, CDCh) 6 1.22 (d, ,7= 6.8 Hz, 3H), 1.41 (s, 9H), 2.53-2.65 (m, 2H), 4.08-4.13 (in, 1H). 4.63 (m, 1H), 9.74-9.75 (m, 1H).
b) 1,1-Dimethylethyl [(l5)-3-(cyclopropylamino) l-methylpropyl]carbamate. The protected diamine was prepared using a modified procedure as described in example Z-32. A solution of 1,1-dimethylethyl [(16)-l-methyl-3-oxopropyl]carbamate (0.178 g, 0.95 mmol) and cyclopropylamine (197 uL, 2.85 mmol) in anhydrous dichloroethane (10 raL) was treated with acetic acid (272 uL, 4.8 mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 20 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give 1,1-dimethylethyl

[(.1.5)-3-(cyclopropylamino)-l-rnethylpropyl]carbamate (0.136 g, 63%) as a clear oil. 'H NMR (400 MHz, CDCb) 8 0.32-0.42 (m, 4H), 1.12 (d, J- 6.8 Hz, 3H), 1.39-1.51 (m, 10H), 1.58-1.92 (m, 2H), 2.05-2.10 (m, 1H), 2,67-2.80 (m, 2H), 3.71 (m, 1H), 4.78 (m, 1H).
c) [(3-S)-3-Aminobutyl]cyclopropylamine dihydrochloride was prepared in a similar manner as described in example Z-29. 'H NMR (400 MHz, CDCla/CDaOD) 8 0.70-0.75 (m, 2H), 0.90-0.94 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H), 1.84-1.94 (m, 1H), 1.97-2.05 (m, 1H), 2.49-2.54 (m, 1H), 2.99-3.04 (m, 2H), 3.23-3.28 (m, 1H).
d)
(4S',12a6)-l-Cyclopropyl-A/-[(2,4-difluoropheiiyl)methyl]-7-hydroxy-4-ai e thy 1-6,8-dioxo-
199

1,2,3,4,6,8, .l2,12a-octahydi'opyrido(r,2':4,5]pyra/>ina[],2-r-?]pyrimidiiie-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0..17 mmol) and free based t(36)'3-aminobutyl]cyclopropylamine (75 mg, 0.59 mmol) were reacted in dichloromethane (2 m.L) with acetic acid to give
(451,12a6Vl-cyclop ropyl-A-[(2,4-difluorophenyl)methyl]-4-me thy 1-6,8-dioxo-7-[(phenyl methyl)oxy]-l,2,3,4,6,8,12,12a-octahydropyrido[l\2':4,5]pyrazino[l,2-<3]pyrimidine-9-carboxamide (74 mg, 80%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give
(4S, 12a-l-cyclopi,-opyl-A/'-[(2,4-difluorophenyl)methyl]'7-hydroxy-4-methyl-6,8-dioxo-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5jpyrazinoll,2-r?Jpyrimidine-9-carboxamide (32 mg, 52%) as an off-white solid. H NMR (400 MHz, CDCla) 6 0.37-0.54 (m, 3H), 0.64-0.70 (m, 1H), .1.35 (d, J= 7.2 Hz, 3H), 1.45-1.49 (m, Hi), 1.76-1.80 (m, 1H), 2.03-2.12 (m, 1H), 2.86-2.93 (m, 1H), 2.99-3.04 (m, 1H), 4.30 (dd, J-A.O, 13.6 Hz, 1H), 4.49-4.67 (m, 4H), 5.00-5.07 (m, 1H), 6.75-6.82 (m, 2H), 7,32-7.36 (m, 1H), 8.28 (s, 1H), 10.4-9 (m. 1H), 12.53 (s, 1H); ES1 MS: 459 (M+l).
Example Z-48:
(45',12a5)-N-[(2.4-Difkiorophenvl)n-iethvll-7-hvdroxv-4-mcthyl-l-f2-(methvloxv)ethvll-6,8-dioxo-l,2,3.4,6,8,12.12a-octahvdropvridofl',2':4.5]pyrazinoll,2'a)pyrimidine-9-carb oxamide.
200

a) [(35)-3-Aminobutyl]l2-(methyloxy)ethyl]amine dihydrochloride. The protected diamine, 1,1-dimethylethyl
((liSM-methyl-3-{[2-(methyloxy)ethyl]amino}propyl)cai-barnate was prepared in a similar manner as described in example Z-47. Subsequently, f(3*S)-3-aminobutyl]l2-(methyloxy)ethyl]amine dihydrochloride was prepared in a similar manner as described in example Z-29. 'H NMR (400 MHz, CDCla/CDsOD) 6 1.21 (d, J= 5.6 Hz, 3H), 1.93 (m, 1H), 2.04 (m, 1H), 2.98-3.05 (m, 4H), 3.22 (m, 2H), 3.26-3.31 (m, 4H), 8.06 (br, < 1 H), 8.81 (br, < 1 H).
b)
(45:i2a6)-AA-K2,4-Difluorophenyl)methyl]-7-hydroxy4-methyl-l-[2-(methyloxy)ethyl]-6,8-clioxo-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':415]pyrazino(l,2-a]pyrimidine-9-cai'b oxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(36)-3-aminobutyl][2-(methyloxy)ethyl]amine (53 mg, 0.37 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(45,,12a6)-AA((2,4-dif]uorophenyl)methylJ-4-methyl-l-(2-(methyloxy)ethyrj-6,8-dioxo-7-KphenylmethyDoxy]-1,2,3,4,6,8,12,12a-octahyd ropyrido(l',2':4,5]pyrazino[l,2-,fl]pyrimi

dine-9-carboxamide (47 mg, 63%) as a film. This material was hydrogenated in a
201

second step as described in example Z-2 to give
(45'l!2a6)-N-((2,4-difluorophenyl)methy]]-7-hydroxy4-methyM-[2-(methyloxy)ethyl]-6
,8'dioxo-1,2,3,4,6,8, 12,12a-octahydropyrido[l\2"4,5]pyrazino[l,2-,2]pyrimidine-9-carbo
xamide (38 nig, 97%) as an off-white .solid. 'H NMR (400 MHz, CDCh) S 1.34 (d, J' =
7.2 Hz, 3H), 1.49 (m, 1H), 2.03-2.12 (m, 1H), 2.67-2.70 (m, 1H), 2.81-2.92 (m, 2H),
3.06-3.15 (m, 1H), 3.30-3.37 (m, 4.H), 3.58-3.63 (m, 1H), 4.20 (dd, J= 3.4, 14,2 Hz, 1H),
4,50-4,59 (m, 1.H), 4.62-4,65 (m, 3H), 5.00-5.03 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37
(m, 1H), 8.27 (s, 1H), 10.46 (s, 1H), 12.54 (s, 1H); ES" MS-- 477 (M+l).
Example Z-49:
i-ace;n/c-(3aS.5aS.13aS)-N-[(2.4-.Difluorophenvl)methvl|-ll-hvdroxv-5-(2-methvlpropvl
)-10,12-dioxo-2,3,3a.4,5,5a,6.10. ISa-decahvdro-lH-cvclopentafelpvridofl'.Slpvi-
a'/inof.l-alpvrimidine-O-cai-boxamide.

a) r<9ce/;j/c-(IS,2S)-2-{[(2-Methylpropyl)annno]methyl}cyclopentanamine
hydrochloride.
In a manner similar to example Z-18a-c, from
jv3ce/jJi'c-(IR,2S)-2-({f(l,l-dimel;hylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic
acid (255 mg, 1.11 mmol) was prepared racemic-], l-dimethylel;hyl
KIS,2S)-2-(aminomethyl)cyclopentyl]carbamate (153 mg, 64 % over 3 steps) as a white
green residue. Reductive amination with isobutyraldehyde followed by deprotection
202

as described in Z-38 steps c and d respectively, gave
ivTce/n/c-(IS,2S)"2'{[(2-methylpropyl)amino]methyl}cyclopentanamine hydrochloride
(105 mg, 39% over 5 steps from amino acid). 'H NMR (methanol-di/CDCb) 8.90
(br s, <1 H), 8.64 (br s, <1 H), 8.28 (m, 1 H), 3.97 (br s, 1 H), 3.37 (m, 1 H), 2.83-2.69
(m, 3 H), 2.18-1.69 (m, 7 H), 0.996 (m, 6 H).
b)
i-acev;7/c-(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methylj-ll-hydroxy-5-(2-meth
ylpropyO-lO.ia-dioxo-a.Sa.S.Sa.e.lO..ISa-decahydro-lH-cyclopentafeJpyridotl'*
:4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide. In a manner similar to that described
in example Z-35, from
j'fl<7e/7j/c-(IS,2S)-2-{[(2-methylpropyl)amino]methyl}cyclopentanamine hydrochloride
105 mg', 0.434 mraol) and 16a (56 rag, 0.119 mmol) was prepared
race/j77'c-(3aS,5aS, 13aS)-N-((2,4-difluorophenyl)methyl]-5-(2-methylpropyD-10,12-diox
o-ll-((phenylmethyl)oxy]-2,3,3a,4,5,5a,6,l0,12,13a-decahydro-lH-cyclopenta(e]pyridof
l',2':4,5]pyrazino(l,2-a]pyrimidine-9-carboxamide (52 mg, 74%). This material was
deprotected in a second step similar to the procedure described in example Z-37.
Thus, from
i,ace/7j/c-(3aS,5aSl13aS)-N-f(2,4-difluorophenyl)methyl]-5-(2-methylpropyl)- 10,12-diox
o-ll-[(phenylmethyl)oxy]-2,3,3a,4,5,5a,6,10,12,13a-decahydro-lH-cyclopentafe]pyridof
l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxam3de (48 mg, 0.081 mmol) and 10% Pd/C
(catalytic amount), the title compound was prepared as a white solid after purification
by HPLC (30 mg, 75%). 'H NMR (CDCh) 12.59 (s, 1 H), 10.42 (s, 1 H), 828 (s, 1 H),
203

7.34 (m, 1 H), 6.79 (m, 2 H), 4.83 (s, 1 H), 4.63-4.68 (m, 3 H), 4.29 (m, 1 H), 4.14 (m, 1
H), 2.91 (m, 1 H), 2.46-2.32 (m, 3 H), 2.15-2.09 (m, 2 H), 1.85-1.61 (m, 5 li). 1.39 (m, 1
H), 0,88 (m, 6 H); ES* MS: 501 (M +1).
Example Z-5Q:
<3J?.lla5)-f(2.4-Difluorophenvl)tnethvll-3-ethvl-6-hvdroxv5.7-dioxo-2.3.5,7.11.11a-h
exahvdro[l.3loxazolQ[3.2-a]pyrido[l,2-t/]pvra2ine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in
example Z-2. 16a (40 mg, 0.09 mmol) and (2i2)-2-amino-l-butanol (0.02 ml, 0.21
mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(3/i,lla6)-A/:[(2,4-difluorophenyl)methyl]-3-ethyl-5,7-dioxo-6-((phenylmethyl)oxyJ-2,3,
5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-r7]pyrido(l,2-rf]pyrazine-8-carboxamide (40 mg',
93%). This material was hydrogenated in a second step as described in example Z-2
to give
(3,lla6)-Af[(2,4-Difiuorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-213,5,7,ll,lla-h
exahydro[l,3]oxazolo[3,2-/7]pyrido[l,2-n']pyrazine-8-carboxamide (30 mg, 91%) as a
white solid. 'll NMR (CDCh) 8 1.1.49 (br, 1 H), 10.28 (m, 1 H), 8.35 (s. 1 H), 7.34
(m, 1 li), 6.79 (m, 2), 5.30 (m, 1 H), 4.62 (m, 2 H), 4.45-4,32 (m, 3 H), 3.93-3.86 (m, 2
H), 2.11 (m, 1 H), 1.65 (m, 1 H), 0.98 (t, J= 7.6 Hz, 3 H); ES+ MS-' 420 (M +1).
204

Example Z51:
i-ace/7;yc-(4aS,6aS,14aS)-N-[(2,4-DifluorQphenvl)methvl]-12-hvdroxy6-(2-(4-morpholin
vl)ethvl]-ll,13-dioxo-l,2.3,4.4a,6,6,6a.7,ll,13J.4a-dodecahvdropyrido[l',2l.4,QJpvi-azin
o[l,2-alquinazoline-10-carboxamide.

a) rscew/cl, 1-Dimethylethyl ((IS,2R)-2-formylcyclohexyl]carbamate. An
alternative procedure from the one given in example Z-38b follows To a solution of
Dess-Martin Periodane (564 mg, 1.33 mmol) in dichloromethane was added
j-ace.Hj/c-l,l-dimethylethyl [(IS,2.R)-2-(hydroxymethyl)cyclohexylJcarbamate (305 mg,
1.33 mmol, see example Z'38a) dropwise as a solution in dichloromethane. The
reaction was stirred 1 hour at ambient temperature until judged complete by TLC (11
hexanes: ethyl acetate KMnO-i stain). The reaction was quenched with aqueous
sodium bicarbonate and sodium thiosulfate solutions, extracted with dichloromethane,
and the combined organics were dried over sodium sulfate. Silica gel
chromatography (0-50% ethyl acetate/ hexanes gradient elution) gave

-racewj/c-l.l-dimcthylethyl l(J.S,2R)-2-formy]cyc)ohexyl]carbamate (280, 93%). See example Z-38b for NMR data.
b) iV7Cfl;jj/i;-{((IS,2S)-2-Aminocyclohexyl]methy]}(2-(4-morpholinyl)ethyl]amine
205

hydrochloride. In a manner similar to that described in example Z-38c-d from i'ace/H/c-l.l-dimethylethyl [(IS,2R)-2-formylcyclohexyl]carbamate (78 rag, 0.344 mmol, prepared using the procedure from example Z-38b) and [2-(4-morpholinyl)ethyl]amine (67 mg, 0.515 mmol) was prepared
jv?ce7;?yc-{KIS,2S)-2-aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 78% over 2 steps) as a white solid. 'H NMR (methanol-A/CDCh) 8.18 (br s, 1 H), 3.84-3,493 (in. 11 H), 3.19-3.119 (m, 5 H), 2.42 (m, 1 H), 2.11 (br s, 2 H), 1.87-1.17 (in, 10 H).
c)
racem;c-4aS,6aS, 14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholiny0ethyl]-ll,13-dioxo-l,2,3,4,4a,5,6,6a,7,l],13,14a-dodecahydi-opyrido(l',2,:4,5]pyrazinofl,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from
j-c,em7'c-{[(IS,2S)-2-aminocyclohexyl]methyl}(2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 0.272 mmol) and 16a (45 mg, 0.0957 mmol) was prepared
2v;c,e;j3/c-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(4-morpholiny!)ethyl]-.ll,13-dioxo-12-[(phenylmethyl)oxy.l-l,2,3,4,4a,5,6,6a,7)ll,13,14a-dodecahydropyridolr,2':4,5]pyrazino[l,2-a]quinazolinel0-carboxamide (27 mg, 43%). This material was deprotected in a second step similar to the procedure described in example Z-37. Fi'om
rflcevn/c-(4aS16aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-(4-morphoUnyl)ethyl]-ll,13-dioxo-12-[(phenylmothyl)oxy]-1,2,3,4,4,5,6,68,7,11,13,14a-dodecahydropyrido[r,2':
206

4,5]pyrazino[l,2-ajquinazoline-10-carboxamide (27 mg, 0.0408 mmol) and 10% Pd/C (1 mg) the title compound was prepared as a white solid after purification by HPLC. JH NMR (CDCh) 12.30 (br s, <1 H), 10.41 (br s, 1 H), 8.29 (s, 1 H), 7.34 (m, 2 H), 6.78 (m, 2 H), 4.76 (m, 1 H), 4.62-4.54 (m, 3 H), 4.29 (m, 2 H), 3,65 (m, 4 H), 3,01 (m, 1 H), 2.76 (m, 2 H), 2.58-2.42 (m, 7 H), 2.21 (m, 1 H), 1.89-1.23 (m, 8 H); ES" MS: 572 (M +1).

Example Z-52:
race w/c<3aR.5&R, 13aS)-N-[(2,4-Difluorophenyl)methy)Hl-hydroxy- 10.12-dioxo-1.2.3.3a,4,5a,6,.10..12,13a-decahvdrocyc]opentafd}pvrido|r.2':4,5i]i3yrazinor21l'blfl,3]oxazine •Q'carboxamide.

a) j'ce/;j/c-l,l-Dimethylethyl ((IS,2R)-2-(hydroxymethyl)cyclopeutylJcarbamate.
vflC0y;j/c-(IR,2S)-2-{(l(l,l-Dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (22 mg, 0.096 mmol) was dissolved in tetrahydrofuran and placed in an ice-water bath. Triethylamine was added, followed by the slow addition of methyl chloroformate. The reaction was stirred ten minutes in the ice-bath and sodium borohydride was added. Methanol was then added slowly and stirring was continued for two hours while the ice-bath expired. 1 M Potassium hydrogen sulfate was added, the reaction was partially concentrated, and product was extracted with dichloromethane. The combined organics were washed with sodium bicarbonate, brine, and dried over sodium sulfate. Removal of solvents under reduced pressure
207

afforded racemic-1,1 -dimethylethy 1 [(IS,2R)-2-(hydroxyraethyDcyclopentyl]carbamate (25 mg, >100%). 'H NMR (CDCla) 4,50 (br s, 1 H), 4.06 (m. 1 H), 3.54 (m. 1 H), 3.37 (m, 1 H), 2.09 (m, 1 H), 1.96 (m, 1 H), 1.64 (m, 3 H), 1.52 (m, 1 H), 1.43 (s, 9 H), 1.11 (m, 2 H).
b) rflce.ra/c"[(IR,2S)-2'Aminocyclopentyl]methanol hydrochloride. In a manner similar to that described in example, from race.m/c-l,l-dimethylethyl [(IS,2R)-2-(hydroxymethyl)cyclopentyl]carbamate and 4 N HC1 was prepared
7'ee;jj/c-[(IR,2S)-2-aminocyc]opentyl]methanol hydrochloride (20 mg, quantitative). >H NMR (methanol-d4-CDCb) 7.76 (br s, <1 H), 3.73 (m, 1 H), 3.61- 3.28 (m, 3 H), 2.27 (br s, 1 H), 2.01 (m, 2.01 (m, 1 H), 1.74-1.70 (m, 2 H), 1.56-1.42 (m, 2 H), 1.16 (br s, 1 H), 1.05 (br s, 1 H).
c)
racemic -(3aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-ll-hydroxy-10,12-dioxo-l,2,3,3a,4,5a,6,10,12,1.3a-decahydrocyclopenta[d)pyrido[l',2l:4,5]pyrazino[21l-b3[l,3]oxazine-9-carboxamide. In a manner similar to that described in example Z-35, from 7VJce/j;/c-[(III,2S)-2-aminocyclopentyl]methanol hydrochloride (20 mg, 0.132 mmol) and 16a (24 mg, 0.051 mmol) was prepared
rce/yc-(3aR,13aS)-N-[(2,4-difluorophenyl) methyl]-10,12-dioxo-ll-[(p he nylme thy l)oxy]-l,2,3,3a,4,5a16,10,.12,13a-decahydrocyclopenta(dJpyridoU,,2,:4,5jpyrazino[2,l-b][l.,3]oxazine-9-carboxamide (7 mg, 26 %) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from
208

l'aceuu'c {3 aR, 13aS)-N-l(2,4-difluorophenyl)methylJ-10,12-dioxo-ll-Kphenylmethyl)oxy]-l,2,3,3a,4,5a,6,10>12,]3a-decahydrocyclopentald]pyrido[r,2,:4,5]pyrazino[2,l-b]ll13]oxazine-9-carboxamide (7 rag, 0.012 mmol) and 10% Pd/C (l mg),
race/;3/'c-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-ll.-hydroxy 10,12-dioxo-l,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[djpyridol.',2':4,5jpyra7-inof2, rb.][l,3]oxazine-9-carboxamide (4 rag, 72%) white solid. »H NMR (CDCla) 12.20 (br s, 1 H), 10.37 (br s, 1 H), 8.31 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.16 (m, 1 H), 4.77 (m, 1 H), 4.64 (m. 2 H), 4.28 (m, 1 H), 4.09 (m, 1 H), 3.97 (m, 1 H), 3.45 (m, 1 H), 2.49-2.20 (m, 2 H), 1.89-1.58 (tn, 4 H), 0.936-0.840 (m, 1 H); ES+ MS: 446 (M +1).
Example Z-53:
7-acew/c-(4aS.6aS,14aS)-N-t(2,4-Difluorophenvi)methvll-12-hvdfoxv6'methvl-11.13-diOXQ- l,2,3,4.4a,5,6,6a,7.11,13,14a-dodecahvdi,opyrido[l'J2'v415]pvra2ino[l,2-a]qiiinayJoli

ne- IQ-carboxamide.

a) r/3ce,/;;/c-{[(IS,2S)-2-Aininocyclobexyl Jmethyl}inethylamine hydrochloride. In a manner similar to that described in example Z-38cd from .race.HJ./c-i.l-dimethylethyl KIS,2R)-2-formylcyclohexyl]carbamate (0.410 mmol) and methyl amine (0.5 mL of a 2 M tetrahydrofuran solution) was prepared j'ace/M/c-{[(IS,2S)-2-aminocyclohexyl]methyl}methy]arnine hydrochloride in two steps as a white solid (46 mg, 53% 2 steps). >H NMR (methanol-rfi/CDCla) 9.05 (br s, 209

H). 8.72
(br s, 4 H), 2.38 (br s, 1 H), 2.07-1.83 (in, 2 H), .1,67-1.14 (m, 6 H).
b)
r/7ce/?j/'c-(4aS,6aS,14aS)-N-[(214-Difluorophenyl) methyl]-12-hydrox}',-6-methyl-lll13-dioxo-l,2,3l4,4a,5,6,6a,7,ll,13,14a-dodecahydropyridolr,2':4,5Jpyrazino[l,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from race/jj/c-{[(IS,2S)-2-aminocyclohexyl]methyl}methylamine hydrochloride (46 nig, 0.215 mmol) and 16a (35 mg, 0.0744 mmol) was prepared
ra comic -(4aS,6aSl14aS)-N-f(2,4-difluorophenyl)methyl]-6-methyl-ll,13-dioxo-12-((phe ny]methyl)oxy]-.l,2,3,4,4a,5,616a,7,ll,13,14a-dodecahydropyrido[l'12':4,5]pyrazinoll,2-a]quinazoline-10-carboxamide(17 mg, 41%) as a white solid. This material was deprotected in s second step similar to the procedure described in example Z'37. Thus, from
racemic •(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methylJ-6-methyl-ll,13-dioxo-12-[(phe nylmethyDoxyJ-l.Sa.S.e.eajaiJS.la-dodecahydropyridofl'..Sjpyrazinot]-a]quinazoline-10-carboxamide (17 mg-, 0,0302 mmol) and 10% Pd/C (l mg) was prepared the title compound as a white solid (9 mg, 64%). 'H NMR (CDClO 10.44 (m, 1 H), 8,29 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.78 (m, 1 H), 4.62 (br s, 2 H). 4.29 (br s, 2 H), 3.41 (s, 1 H), 2.92 (m, 1 H), 2.66 (m, 1 H), 2.35-2.25 (m, 4 H), 1.90-1.74 (m, 2 H), 1.67-1.24 (m, 6 H); ES+ MS: 473(M +1).
Example Z-54:
210

ragem.?c-(4aS.6aS.14aS)-N-[(2,4-Difluorophenvl)iTiethvl]-12-hvdroxv-6-|"2-(methvloxv)ethvl]-ll.13-diQXQ-1.2.3.4.4a.5.6,Ga.7.11,1.3,.14a-dodecahvdropvridol'l'.2l:4.5lpvrazinoll.2-alquinazoiine-lQ-carboxamide,

a) iV3cevwiC-{[(IS,2S)-2-Aramocyclohexyl]meth3'l}f2-(mefchyloxy)ethyl]amine hydrochloride.
In a manner similar to that described in example Z-38c-d from race,H2/c'l,l-dimethylethyl [(IS,2R)-2-formylcyclohexyl]carbamate (93 nig, 0.410 mmol) and [2'(methyloxy)ethyl]amine (0.05 ml, 0.615 ramol) was prepared in two steps race.m/c-{[(IS,2S)-2-aminocyclohexyl]methyl}[2- (me thyloxy)ethyl] amine hydrochloride (63 mg, 60% 2 steps) as a white solid. >H NMR (methanol-flVCDCIs) 9.02 (br s, <1 H), 8.78 (br s, <1, H), 8.29 (br s, 1 H), 3.69 (br s, 2 H), 3.46)s, 3 H), 3.36-3.18 (m, 4 H), 2.97 (br s, 1 H), 2.46 (br s, 1 H), 1.86-1.40 (in, 8 H).
b)
jce;;j/c-4aS,6aS,14aS)-N-[(2,4-'Difluorophenyl)methyrj-12-hydroxy6-[2-(methyloxy)ethyl)-ll,13dioxo-l,2,3,4,4a)5,6,6a,7,ll,13,14a-dodecahydropyridolr,2':4,5]pyrazino(.l,2-a]quinazohne-10-carboxamide. In a manner similar to that described in example Z-35, from
i-acevjj/c-{[(IS,2S)-2-aminocydohexyl]methyl}[2-(methyloxy)ethyl]amine hydrochloride (63mg. 0.244 mmol) and 16a (40 mg, 0.0851 mmol) was prepared
21]

i'ace/yc-(4aS,6aS,14aS)-N-((2,4-difluoraphenyl)methyl]-6-[2-(methyloxy)ethyl]-ll,13-dioxo-12-f(phenylniethyl)oxy]-ll2,3,4,4a)516>6a,7)ll,13114a-dodecahydropyrido[l,,2,:4,5]pyraxino[l,2-a]quinazoline-].0-carboxamide (44 mg, 8.1%) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from racemjc-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-l2-(methyloxy)ethyl]-ll,13-dioxo-12-((phenylmethyDoxyl-l.Sa.S.e.ea.ll.IS.Ha-dodecahydropyridofl'.Slpyrazino[l,2-a]quinazoline-10-carboxamide (44 mg, 0.0726mmol) and 10% Pd/C (l mg) the title compound was prepared as a white solid (37 mg, quantitative). 'H NMR (CDCb) 12.60 (br s, 1 H), 10.47 (m, 1 H), 8.28 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.81 (m, 1 H), 4,64 (m 3 H), 4.51 (m, 1 H), 4,26 (m, 1 H), 3.63 (m, 1 H). 3.31 (s, 3 H), 3.19 (m, 1 H), 2.86 (m, 1 H), 2.67 (2m, 2 H), 2.21 (m, 1 H), 1.91-1.78 (m, 2 H), 1.671.52 (m, 4 H), 1.46-1.24 (m, 3 H); ES- MS'- 517 (M +l).
Example Z~55:
i'ace;;?/c-(4aS.6aS.14aS)-6-[2-(Acetvlamino)ethyl]-N-[(2,4-difluQrophenvl)methvl]-12hvdroxvll.l3'dioxo-1.2,3.4.4a.5.6.6a.7.11.1.3,14a-dodecahydropyrido[l',2'-4,5]pyrazino|1..2-a]quinazoline-10'carboxamide.

a) vviC6'ra/c-N-l2-({l(IS,2S)-2-Aminocyclohexyl]methyl}amino)ethyl]acetamide
212

hydrochloride. In a manner similar to that described in example Z"38c-d from racera/c-l.l-dimethylethyl [(IS,2R)-2-formylcyclohexyl]carbamate (93 mg, 0.41 mmol) and N-(2-aminoethyl)acetamide (63 mg, 0.615 mmol),
i-ara/c-N-[2-({[(IS,2S)-2-aminocyclohexy lime thy l}amino)ethyl] ace tamide hydrochloride was prepared in two steps as a white solid (82 mg), 71% 2 steps).]H NMR (methanol-rfi/CDCh) 8.86 (br s, 1 H), 8.29 (br s, 1 H), 3.62-3.51 (m, 3 H), 3.40-3,28 (m, 4 H), 3.22-2.93 (m, 3 H), 2.47 (m, 1 H), 2,08-2.06 (m, 4 H), 1.83-1.75 (in, 2 H), 1.56-1.44 (m, 3 H), 1.23 (m, 1 H).
b)
i-acej/c-4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methy

11-12-hydroxy 11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13, Ha-dodecahydropyridod'-.SIpyr azinofl,2-a]quinazolinel0-carboxamide. In a manner similar to that described in example Z-35, from j-5ceraic-N-[2-({[(IS,2S)-2-aminocyclohexyl]methyl}amino)ethyl]acetamide hydrochloride (82 mg, 0.349 mmol) and 16a (50 mg, Q.106 mmol) was prepared the title compound (24 mg, 36%). This material was deprotected in a second step similar to the procedure described in example Z-.37. Thus, from racemic (4aS,6aS,14aS)-6-[2-(acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-II,13-dioxo-l 2-[(phenylmethyl)oxy]-l,2,3,4,4a,5,6,6a,7,II,13114a-dodecahydropyrido[r,2'M,5]pyrazi no[l,2-a]quinazoline-10-carboxamide (24 mg, 0.0379 mmol) and 10% Pd/C (l mg) was prepared the title compound as a white solid after purification by HPLC. IH NMR (CDCU) 12.59 (s, 1 H), 10.44 (s, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6,79 (m. 2 H), 5.86
213

(s, 1 H), 4.78 (m, 1 H), 4.61-4.50 (m, 3 H), 4.30 (m,] H), 3.35 (m, 1 H), 3.18 (m, 1 H), 2.96 (m, 1 H), 2.76 (m, 2 H), 2.48 (m, 1 H), 2.19 (m, 1 H), 1.89-1.23 (rn, 12 H); ES+ MS:544(M+1).
Example Z-56"
(35,3.1a/f)'N-f(2.4-Difluoi-o»henvl)methvl]-3-ethvl-6-hvdroxv-5,7-dioxo-2,3.5.7.II.IIa-h exahvdro[l,3}oxazolo[3,2-1pyrido[l,2-(7lpvrazine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (25)-2-amino-l-butanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (35,IIa./?)-A[(2,4-difluorophen.yl)methyl]-3-ethyl-517-dioxo-6-[(phenylmethyl)oxy]-2,3, 5,7, II,IIa-hexahydroll,3]oxazolo[3,2-a]pyrido[l,2-n']pyrazine-8-carboxamide (39 mg, 90%). This material was hydrogenated in a second step as described in example Z-2 to give
(35,IIaA)-N-[(2,4-difluorophenyl)methyl]-3-ethyl-6-hydi-oxy-5,7-dioxo-2,3,5,7,II,IIa-h exahydro[l,3]oxazolo[3,2-.dpyrido[l,2-fl']pyrazine-8-cai'boxamide (37 mg, 99%) as a tinted white solid. >H NMR (CDCla) 6 11.47 (br, 1 H), 10.26 (m, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.77 (m, 2), 5.29 (m, 1 H), 4.60 (m. 2 H), 4.47-4.32 (m, 3 H), 3.93-3,85 (m, 2 H), 2.08 (m, 1 H), 1.68 (m, 1 H), 0.95 (t, J= 7.6 Hz, 3 H); ES+ MS: 420 (M +1).
214

(s, 1 H), 4.78 (m, 1 H), 4.61-4.50 (m, 3 H), 4.30 (m, 1 H), 3.35 (m, 1 H), 3.18 (m, 1 H), 2.96 (ra, 1 H), 2.76 (m, 2 H), 2.48 (m, 1 H), 2.19 (m, 1 H), 1.89-1.23 (ra, 12 H): ES< MS:544(M+1).
Example Z-56:
(3'.IIa/)-iV'f(2.4-DifluoroDhenvl)iTiethvl]-3-ethvl-6-hvdroxv-5.7-diQxo'2.3.5.7.11.11a-h exahydro[l,3]oxazolo[3,2-,dpyrido[l,2-tf|pvrazine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 nig, 0.09 mmol) and (2i5!>-2-amino-l-butanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (36',IIa./2)-A[(2,4-difluoiophenyl)methyl]-3-ethyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3, 5,7,II,IIa-hexahydroll,3]oxazolo[3,2-fi]pyridoll,2-fl']pyi-azine-8-carboxamide (39 rag, 90%). This material was hydrogenated in a second step as described in example Z"2 to give
(36',IIaAJ)-Ar-[(2,4-dif]uorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,II,IIa-h exahydro[l,3]oxazolof3,2-a.lpyrido[l,2-o']pyrazine-8-cai'boxamide (37 mg, 99%) as a tinted white solid. >H NMH (CDCla) 5 11.47 (br, 1 H), 10.26 (m, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.77 (m, 2), 5.29 (ra, 1 H), 4.60 (m, 2 H), 4,47-4,32 (m, 3 H), 3.93-3.85 (m, 2 H), 2.08 (m, 1 H), 1.68 (m, 1 H), 0.95 (t, /= 7.6 Hz, 3 H); ES" MS: 420 (M +1).
214

Example Z-57:
(35.11a.fl)-3-Butvl-Ar(2.4-clifluorophenvl)methvl]-6-hvdroxv5.7-dioxo-2.3.6.7.11.11a-h exahydro|.l,3loxazolo[3,2-,'jjpyridon,2-qr]pvrazine-8-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2 reacted in dichloromethane (2 mL) with acetic acid to give (3,llayj)-3-butyl-Ar-l(214-dinuorophenyl)me(,hyl]-5,7-dioxo.-6-((phenylmethyl)oxy)-2,3, S.T.II.IIa'hexahydvotl.SJoxazololS'flJpyridotl-rfJpyrazine-S-carboxamide (43 mg, 94%). This material was hydrogenated in a second step as described in example Z-2 to give
(35,,Ua7J)-3-butyl'A';[(2l4-difluorophenyl)methyl]-6-hydroxy5,7-dioxo-2l3,6l71ll1lla-h exahydrofl ,3]oxazolo[3,2fl]pyrido[],2c/]pyrazine-8-carboxamide (33 mg, 92%) as a tinted white solid. >H NMR (CDCla) 6 11.48 (br, 1 H), 10.27 (br, 1 H), 8.36 (br, 1 H), 7.31 (m. 1 H), 6.77 (m, 2), 5.28 (m, 1 H), 4.59-4.36 (m, 5 H), 3.83 (m, 2 H), 2.08 (m. 1 H), 1.58 (m, 1 H), 1.39-1.23 (m, 4 H), 0.90 (t, /= 6.8 Hz, 3 H); ES' MS: 448 (M+l).
Example Z'58:
(36'.lla)-A-l(2.4-Difluorophenvl)methvll-6-hvdroxv3-K4-hvdroxyphenyl)methvli-5.7-dioxo-2,3,5.7,11,1 la-liexahydrot 1,3] oxazolo[3,2-lpyrido[l, 2-alp yrazine'8-carboxamide
215

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 rag, 0.09 mmol) and 4-[(2£V2'amin (43 mg, 0.21 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give
(3£;ilai?)-iV-[(2,4-difluorophenyl)methyl]-3-f(4-hydroxyphenyl)methylJ-517-dioxo-6-[(p henylmethyl)oxy)'2,3,5,7,II,IIa-hexahydro[l,3]oxazolo[3,2-aJpyrido[l,2-a']pyrazine-8-c arboxamide (10 mg, 20%). This material was hydrogenated in a second step as described in example Z'2 and purified via preparative HPLC to give
(36,,]la/d-AcK2,4-difluorophenyl)methyl]-6-hydroxy3-((4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7, II,IIa-hexahydro[l,3]oxazolo [3,2-/i]pyridot 1,2- (7 mg, 63%) as a white solid. »H NMR (CDsOD) 5

dioxo-2,6,6,7, 11,11a-hexahydro[1,3]oxazolo [3,2-]]pyridot 1,2- (7 mg, 30%) as a white solid. »H NMR (CDSOD) 6
10.43 (m, 1 H), 8.34 (s, 1 H),
7.33 (m, 1 H), 7.00 (d, /= 8.4 Hz, 2 H), 6.82 (m, 2 H), 6.71 (d, /= 8.4 Hz, 2 H), 5.05 (m,
1 H), 4,67-4.57 (m, 4 H), 4.21 (dd, J = 8.8, 7.2 Hz, 1 H), 3.94 (dd, J- 8.8, 6.4 Hz, 1 H),
3.21 (dd, J- 13.2, 3.2 Hz, 1 H), 2.90 (dd, ,/ = 13.6, 8.8 Hz, 1 H); ES+ MS: 498 (M+l).
Example Z-59:

(4S.12aS)-l-Cyclobutvl-N-f(2,4-difluorophenvl)methvn-7-hvdroxv-4-i-nethvl-6,8-dioxo-.l
,2,3.4.6,8.12,12a-octiahydropyridofr,2':4,5]pyrazino[l.2-alpyrimidine-9-carboxamide.
216

a) l(3SV3-Aminobutyl]cyclobutylamine dihydrochloride was prepared in a similar
manner as described in example Z-47. >H NMR (400 MHz, CDCI3/CD3OD) S 1.23 (d,
/= 6.4 Hz, 3H), 1.69-2.26 (m, 8H), 2.83 (m, 2.H), 3.31-3.33 (m, 1H), 3.55 (m, 1H), 8.08
(br, <1H), 9.07 (br, <1H).
b)
(4',12a5)-l-Cyclobutyl-A[(214-difluoropheiiyl)methyl)-7-hydroxy-4-methyl-6,8-dioxo-l
l2,3,4,6,8l12,12a-octahydropyrido[l',2,:4l5]pyrazino[.l,2-]pyrimidine-9-carboxamide.
The title compound was made in two steps using a similar process to that described in
example Z-2. 16a (80 mg, 0.17 minol) and free based
f(36)-3-aminobutylJcyclobutylamine (96 mg, 0.68 mmol) were reacted in
dichloromethane (2 mL) with acetic acid to give
(46',12a6)-l-cyclobutyl-N-[(2,4-difluorophenyl)methy])-4-methyl-6,8-dioxo-7-[(pheiiylm
ethyl)oxy]-l,2,3,4,6,8,12,12a"Octahydropyridofr,2'.'4,5]pyi'azino[l,2-a]pyrimidine-9-car
boxamide (68 mg, 70%) as a film. This material was hydrogenated in a second step
as described in example Z-2 to give
(4S,,12a5)-l-cyclobutyl-A,-f(2,4-difluorophenyl)met.hyl]-7-hydrox.y-4-methyl-6,8-dioxo-l
,2,3,4,6,8,12,12a-octahydropyrido[ri2':4,5]pyrazino[l,2-fl]pyrimidine'9-carboxamide
(57 mg, 100%) as an off-white solid. »H NMR (400 MHz, CDC13) 6 1,31 (d, J= 6.8 Hz,
3H), 1.46-1.70 (m, 4H), 1.91-2.12 (m, 4H), 2.52 (m, 1H), 2.90-2.93 (m, 1H), 3.06 (m,
217

1.H), 4.16-4.29 (m, 3H), 4.57-4.66 (ra, 2H), 4.99-5.05 (m, 1H), 6.75-6.82 (in, 2H),
7.32-7.38 (m. 1H), 8.20 (s, 1H), 1.0.44 (s, 1H), 12.51 (s, 1H); ES+ MS: 473 (M+l).
Example Z'6Q:
(45.12a)-Af(2,4-.DifluQrQphenvl)methyl]-7-hvdroxv-4-methyl-6,8-dioxo-l-(tetrahvdi-o-
2/f-thiqpvran-4-vl)-1.2.3.4.6.8.12.12a-octahvdropvridofr.2':4.5jpvrazino|l,2-)pvrimid
ine'9-cai'boxaiTiide.

a) [(3iS-,3-Aminobutyl]tetrahydro-2j?7-thiopyj:an-4-ylamine dihydrochloride was
prepared in a similar manner as described in example Z"47.]H NMR (400 MHz,
CDCU/CDsOD) S 1.21 (d, J- 6.4 Hz , 3H), 1.65-1,75 (m, 2H), 1.90-2.10 (m, 2H), 2.35
(m, 2H), 2.56-2.61 (m, 4H), 2.92-2.98 (m, 3H), 3.27-3.31 (m, 1H), 8.05 (br, <1H), 8.90
(br, <1H).
b)
(45'112a6)-N-[(2,4-difluorophenyl)methyl]-7-hydroxy4-methyl-6,8-dioxo-.l-(tetrahydro-
2-thiopyran-4-y!)-l,2,3,4,6,8,12,12a-octahydropyrido(l,,2':4,5]pyrazino[l,2-]pyrimid
ine-9carboxamide. The title compound was made in two steps using a similar
process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based
[(3S)-3-aminobutyl]tetrahydro-2H-thiopyran\4-ylamine (108 mg, 0.58 mmol) were
reacted in dichloromethane (2 mL) with acetic acid to give
218

(45,12aiS!)-AA-((2,4-difluorophenyl)met.hyl]-4-i-ncthyl-6,8-dioxo-7-l(pheriylmcthyl)ox.y3'l-
(tetrahydro-2N:thiopyvan-4-yl)-l,2,3,4,6,8,12,12a-octahydropyridofl',2'-'4,5]pyrazino[l,
2-a]pyrimidine-9-carboxamide (56 mg, 54%) as a film. This material was
debenzylated in a second step to in a manner similar to Z-26 to give
(46,,12a6)-7V-[{2,4-difluorophenyl)methyl]-7-hydroxy4-methyl-6,8-dioxo-l-(tetrahydro-
2i7-thiopyran-4-yl)-l,2,3,4,6,8)12112a-octahydropyridol.l',2':4,5]pyrazino[l,2-a]pyrimid
ine-9-carboxamide (56 mg, >100%) as an off-white solid. IH NM.R (400 MHz, CDC13)
6 1.30 (d, J= 6.8 Hz , 3H), 1.54-1.58 (m. IH), 1.72-1.82 (m, 3H), 1.97-2.11 (m, 2H),
2.60-2.76 (5H), 2.86 (m, 2H), 4.17-4.30 (m, 2H), 4.62-4.66 (m, 3H), 4.92-4.96 (m, IH),
6.75-6.82 (m, 2H), 7.32-7.38 (m, IH), 8.31 (s, IH), 10.46 (s, IH), 12.48 (s, IH); ES+
MS: 519 (M+l).
Example 2-61:
(46',12a6)-iV-f(214-Difluoi-ophenvl)methvn-7-hvdroxy-l,4-bis(2-methvlpropvl)-6,8-dioxo
-l,2.3.4.6,8,12,12a-octahvdroi)vridofr.2':4,5lpvrazinof.l.2-a)pvrimidine-9-carboxamide.

a) [(3-3-Amino-5-methylhexyl](2-methylpropyl)amine dihydrochloride was
prepared in a similar manner as described in example Z-32. rH NMR (400 MHz,
CDCla/CDaOD) 8 0.87 (d, J= 6.4 Hz ,611), 0.97 (d, ,7= 6.8 Hz , 6H), 1.34-1.41 (m. IH),
.1.45-1.52 (m, IH), 1.58-1.66 (m, IH), 2.01-2.13 (m, 2H), 2.72-2.73 (in, 2H). 3.03-3.06
219

(m. 2H), 3.29 (m, 2H), 8.07 (br, <1H), 8.71 (br, <1H).
b)
(46',]2a6)-N-[(2,4-Difluorophenyl)methyl]-7-hydroxy-l,4-bis(2-methylpropyl)-6,8-dioxo
•1,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]py].'azino(1,2'fljpyi'imidiae-9'carboxaimde.
The title compound was made in two steps using a similar process to that described in
example Z-2. 16a (80 mg, 0,17 raraol) and free based
t(3S)-3-amino-5-methylhexyl](2-methylpropyl)amine (117 mg, 0.63 mmol) were
reacted in dichloromethane (2 mL) with acetic acid to give
(4S, 12a6)-A-[(2,4-difluorophenyl)methyl]-l,4-bis(2-methylpropyl)-6,8-dioxo-7- [(phenyl
methyl)oxy]-],2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-a]pyrimidine-9-c
arboxamide (68 mg, 66%) as a film. This material was hydrogenated in a second step
as described in example Z-2 to give

(45,,12a5)-iV-((2,4-difluorophenyl)methyl]-7-hydroxy-l,4-bis(2-methylpropyl)-6,8-dioxo-
1,2,3,4,6,8,12,12a-octahydi-opyrido[l',2':4,5]pyrazino[l, 2-a]pyrimidine-9carboxamide
(56 mg, 97%) as an off-white solid. 'H NMll (400 MHz, CDC13) 8 0.74 (d, /= 6.4 Hz,
3H), 0.84 (d, J- 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.83 (m, 511), 2,03-2.12 (in, 2H),
2.21-2.28 (in, 1H), 2.77 (m, 1H), 2.90-2.93 (m, 1H), 4.19-4,40 (m, 3H), 4.59-4,70 (m,
2H), 4.96-4,97 (in, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, 1H), 1.0.47 (s, 1H),
12,59 (br, 1H); ES+ MS: 517 (M+l).
Example Z-62:
j,flCG/7;/c-(4aS.6aS,14aS)-N-[(2.4-Difluorophenvl)methvl1-12-hydroxv6-(2-hvdroxvethvl
220

)'ll,13-dioxo-1.2.3.4,4a,5,6.6a.7.11.13,14a-dodecahvdronvridofr,2':4,5]pvrazinof.l.2-a3
quinazoline-lO'carboxamide,

a) rac In a manner similar to that described in example Z'55a, from
race;jj/c-l,l-dimethylethyl [(lS,2R)-2-formylcyclohexy!]carbamate (112 mg, 0.431
mmol) and 2-aminoethanol (0.04 raLm 0,746 mraol) was prepared
iWce/Hi'c-2-({[(iS,2S)-2-aminocyclohexyl]methyl}amino)ethanol bis •hydrochloride in
two steps (102 mg, 84% over 2 steps). < 2 H), 8.16 (br s, 1 H), 4.02-3.93 (in, 2 H), 3.80 (br s, 2 H), 3.53 (m, 1 H),
3.36-2.93 (m,
6 H), 2.41 (br s, 1 H), 2.05 (in, 1 H), 1.75-1.41 (m, 4 H).
w
raceOTyc-(4aS,6aS(14aS)-N-l(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydr
oxyethyl)-ll,13-dioxo-l,213l4)4a,5,6l6a,71ll,13114a-dodecahydropyrido[l',2':415]pyrazi
no[l,2-a]quinazoline-10-carboxamide. In a manner similar to that described in
example Z-35, from 16a (45 mg, 0.0957 mmol) and
v- 0,418 mmol) was prepared
i'flce7jj;c-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl)-6(2-hydi-oxyethyl)-ll,13-dioxo
-12-[(phenylmethy0oxy]-l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyridoll,,2"-4,5]pyra
221

zino[l,2-a]quinazoline-10-carboxamide (7 mg, 12 %) as a white solid after silica gel
chromatography (1-12% methanol/dichloromethane gradient elution). This material
was deprotected in a second step similar to the procedure described in example Z-37.
Thus, from
rflce;j2/'c-(4aS16aS,14aS)-N-f(2,4-difluorophenyl)methyl)-6-(2-hydroxyethyl)-ll,13-dioxo
-12-t(phenylmethyl)oxy]-l,2,3,4,4a,5,6,6a,7,.U,13,.14a-dodecahydropyrido[r,2':4,5]pyra
zino[l,2-a]quinazoline-10-carboxamide (7 mg, 0.0118 ramol) the title compound was
prepared after purification by HPLC (3 mg, 50 %). »H NMR (CDCla) 12.57 (br s, 1
H), 10.45 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.80 (Hl, 1 H), 4.71 (s, 1
H), 4.62 (m, 2 H), 4,44 (m, 1 H), 4,33 (m, 1 H), 3.75 (m, 1 H), 3.62-3.20 (m, 3 H), 3.13
(m, 1 H), 2.74-2.71 (m, 2 H), 2.24 (m, 1 H), 1.90-137 (m, 12 H), 1,271.23 (m, 3 H)1.12
(m, 1 H); ES+ MS: 503 (M +1).
Example Z-63:
i-acg;73i'c-(4aS,6aS,14aS)-6'Cvclopropyl-N-[(2,4-difluorophenyl)methvll-12-hvdroxv-1.1.1
3-dioxo-1.2,3.4,4a,5.6,6a,7,ll,13,14a-dodecahvdroDvridolr.2".4.5lpvrazinofl.2-alquina
zoline- 10-carboxamide.

a) j-ace;ju'c-(IS,2S)-2-[(Cyclopropylamino)methyl]cyclohexanamine hydrochloride.
In a manner similar to that described in example Z-55a, from
i72ce.m;c-l,l-dimethylethyl KIS,2R)-2-fovmylcyclohexyl]carbamate (112 mg, 0.497
222

mmol) and cyclopropylamine (0.05 mL, 0.746 mmol) was prepared
7-ace;7Jic-(IS,2S)-2,[(cyclopropylamino)methyl]cyclohexanamine bis hydrochloride salt
in two steps (102 mg, 86% over 2 steps). This material was used without further
purification. >H NMR (methanol-A/CDClj) 8.31 (br s, 1 H), 3.75 (br s, 1 H), 3.54
(m, 1 H), 2.96 (m, 1 H), 2.71 (m, 1 H), 2.27 (m, 1 H), 1.94 (ra, 1 H), 1.76-1.15 (m, 8 H),
0.88-0.78 (m, 3 H).
b)
iVice/jj/ roxylll13-dioxo-l,213,4,4a,516,6a,7>ll,13,14a-dodecahydropyrido[r,2l:4J5]pyrazino[l,
2-a]quinazoline-10-carboxamide. In a manner similar to that described in example
Z-35, from 16a (45 mg, 0.0957 mmol) and racemic
(IS,2S)-2-[(cyclopropylamino)methyl]cyclohexanamine hydrochloride (102 mg, 0.425
mmol) was prepared
rc0i;2/c-(4aS,6aS,14aS)-6-cyclopropyl-N-l(2,4-difluorophenyl)methyl]-ll,13-dioxo-12-((
phenylmethyl)oxy]-l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[l',2"4,5jpyra7,ino[
l,2-a]quinazoline-10-carboxamide as a white solid after silica gel chromatography
(1-12% methanol/dichloromethane gradient elution). This materia] was deprotected
in a second step similar to the procedure described in example Z-37. Thus, from
race;2iyc-(4aS,6aS, 14aS)-6-cyclopi-opyl-N-[(2,4-difluorophenyl)methyl]-1], 13-dioxo-12-f(
phenylmethyl)oxy]-l,2,3,4,4a,5,6,6a,7,ll, 13,14a-dodecahydropyrido[l\2'-'4,5]pyrazino[
l,2-a]quinazoline-10-carboxamide (56 mg, 0.0949 mmol) the title compound was
prepared as a white solid (41 mg, 81%). iH NMR (CDCla) 12.10 (br s, < 1 H), 10.45
223

(m, 1 H), 8.27 (s, 1 H), 7.33 (m, 1 H), 6.88 (m, 2 H), 4.77 (m, 1 H), 4.61-4,49 (m, 4 H),
4.33 (m, 1 H), 2.94 (m, 1 H), 2.79 (m, 1 H), 2.17 (m, 1 H), 1.86-0.86 (m, 10 H), 0.658 (m,
1 H), 0.499-0.32 (m, 2 H); ES+ MS: 499 (M +1).
Example Z-64:
vacemic •(4aS,6aS.14aS)-N-f(2,4-pifluoropheuvl)methvi]-12-hvdroxy.U.13-dioxo-6-l2-(
1-pvrrolidinyDethvl)-1.2,3,4.4a,5.6.6a, 7,11,13, 14a-dodecahydropyridof r,2':4,5,]pvrazin
o[l,2-a.lquinazoline-lQ-carboxamide formic acid salt

a) i,sceyjj/c-(IS,2S)-2-({[2-(l-Pyri-olidinyl)ethyl]amino}methyl)cyclohexanamine
hydrochloride. In a manner similar to that described in example Z-55a, from

hydrochloride. In a manner similar to that described in example Z-55a, from race;jj/c-l,l-dimethylethyl [(IS,2R)-2-formylcyclohexyl]carbamate (112 mg, 0.497 mmol) and 2-(l-pyrrolidinyl)ethanamine (0.09 mL, 0.746 mmol) was prepared race/7j/c-(IS,2S)-2-({[2-(l-pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine (88 mg, 60% 2 steps) as the bis hydrochloride salt in two steps as a white solid. 'H NMR (methanol-tfi/CDCh) 9.68 (br s, < 1 H), 9.24 (br s, < 1 H), 8.25 (br s, 1 H), 3.75- 3.04 (m, 11 H), 2.37 (br s, 1 H), 2.06-1.20 (m, 12 H).
b)
rae 224

xo-6-(2-(l-pyrrolidinyl)ethyl]-l,2,3,-1,4a,5,6)6a,7,ll,13,14a-dodecahydropyridofr,2,:4,5] pyra'zino[l,2-a]quinazoline-10-carboxamide formic acid salt.
In a manner similar to that described in example Z-35, from 16a (30 mg, 0.0638 mmol) and
i'fl£,e;73/c-(IS,2S)-2-({[2-(l-pyrrolidinyl)c(.hyl]amino}methyl)cyclohexanamine hydrochloride (88 mg, 0.296 mmol) was prepared
i'ace;;j/c-(4aS,6aS,14aS)-N-[(2,4-difli!orophenyl)methyl]-llF13-dioxo-12-l(phenylmethyl)oxy]-6-[2-(l-pyrrolidinyl)ethylJ-l12,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[l',2': 4,5]pyrazino[l,2-a]quinazoline-10-carboxamide as a white solid (31 mg, 76%) after silica gel chromatography (1-12% mcthanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37, Thus, from
race/J37C-(4aS,6aS,14aS)-N-({2l4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenyl methyl)oxy]-6-[2-(l-pyrrolidinyl)ethylJ-l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[r,2'-' 4,5]pyrazino[l,2-a)quinazoline-10-carboxamide (31 mg, 0.048 mmol) the title compound was prepared as a yellow solid after purification by HPLC (18 mg, 66%). 'H NMR (CDCla) 10.39 (br s, 1 H), 8.56 (br s, 1 H), 8.39 (br s. 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4,76-4.40 (m, 6 H), 3.26-2.89 (m, 7 H), 2.73 (m, 1 H), 2.15 (m, 1 H), 2.02-1.18 (in, 14 H); ES+ MS: 556 (M +1).
Example Z-65:
(4aS,14aS)-N-[(2,4-Difluorophenvl)methyl]-9-hvdrQxv8,]0-dioxo-2,3,4,4a,5,6.8.10,14.1 4a-decahvdro-lH-pvridofl,2-c]pvrido[r.2':4,5lpvrazinof] ,2-a]pvrimidine-l 1-carboxami
225

a) {2-[(2S)-2-Piperidinyl]ethyl}amine. This compound was prepared in a similar manner as its cnantiomer described in example Z*42a,
b)
(4aS,14aS)-N-[(214-Difluorophen.yl)methyll-9-hydroxy8,10-dioxo-2J3,4,4a,5,6, 8,10,14,14a-decahydro-lH-pyrido(l,2"c]pyrido[]',2':4,5]pyi'azinoti,2-ajpyrimidine-3] -c arboxamide. In a manner similar to that described in example Z-35, from {2-[(2S)-2-piperidinyl]ethyl}amine (28 rag, 0.218 mmol) and 16a (30 mg, 0.0638 mmol) was prepared
(4aS,14aS)-N-[(2,4-difluorophenyl)methyl]-8,]0-dioxo-9-[(phenylmethyl)oxy]-2,3,414a,5 ,6,8,10,14, Ha-decahydro-lH-pyrido[l,2-c]pyrido[r,2':4,5]pyrazino[l,2'a]pyrimidine'U -carboxamide (29 mg, 82%) . This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid (26 mg, quantitative). >H NMR (CDCh) 5 12.44 (br s, 1 H), 10.48 (s, 1 H), 8.26 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 4.68-4.67 (m, 2 H), 4.38 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1H), 3.63-3.39 (m, 2 H), 2.91 (m, 2 H), 2.29 (br s, 1 H), 2.02 (m, 1 H), 1.69-1.45 (m, 4 H), 1.30-1.24 (m, 2 H), 1.12 (br s, 1 H); ES- MS: 459 (M+l).
226

Example Z-66:
(4S,.12aS)-N-[(4-Fh.iorophenvl)methvl]-7-hvdroxv-4-methvl-l-f2-(methvloxv)ethyll-6,8-dioxo-l,2,3,4,6,8,].2,12a-octahvdropvridolr,2':4.5lpvrazinofl,2-alpvi'imidine-9-carboxa mide.

a) [(3S)-3-Aminobutyl][2-(methyloxy)ethyl]arnine bis hydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl [(IS)'l-methyl'3-oxopropyl]carbamaf.e (76 mg, 0.406 mraol) and 2-(methyloxy)ethyl]amine (0.05 mL, 0.609 ramol) was prepared ((3S)-3-aminobuty]]l2-(meth3'loxy)ethylJamine as the bis hydrochloride salt in two steps (19 mg, quantitative). 'H NM.R (methanol-rfi/CDCl3) 5 9.02 (< 1 H), 8.21 (< l H), 3.68 (br s, 2 H), 3.49 (br s, 1 H), 3.34 (br s, 4 H), 3.15 (br s, 4 H), 2.26-2.11 (ra, 2 H), 1.35 (br s, 3 H).
b)
(4S112aS)-N-[(4"Fluorophenyl)methyl]-7-hydroxy-4-methyl-l'[2-(methyloxy)et hy6,8-dioxo-l,2,3,4,6,8,12,12a-octahydropyrido[l\2':4,5jpyra7Jnoll,2-a]pyrimidine-9 -carboxamide. In a manner similar to that described in example Z-35, from 16 (15
227

mg, 0.034 mmol) and [(3S)-3-Aminobufcyl][2-(methyloxy)ethyl]amine bis hydrochloride (19 mg, 0.087 mmol),
(4S,12aS)-N-[(4-fluorophenyl)methyJ]-4-mefchy]-l-[2-(methyloxy)ethyl]-6,8-dioxo-7-[(ph enylmethyl)oxy]-l,2,3,4,6,8J2,12a-octahydropyrido[l\2':4,5jpyrazino[l,2-a]pyrirnidine -9-carboxamide was prepared as a white solid after silica gel chromatography (1-12% methanol/dichloromethane). This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a yellow solid (9 mg, 60 %, 2 steps). >H NM.R (CDCIs) 6 12.56 (s, 1 H), 10.51 (m, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.98 (m, 2 H), 5.03 (m,] H), 4.65-4.59 (m, 2 H), 4.53 (m, 1 H), 4.2J. (m, 1 H), 3.61-3.40 (m, 2 H), 3,34-3.13 (m, 3 H). 3.08 (m, 1 H), 2.94-2.84 (m, 2 H), 2.68 (m, 1 H), 2.07 (m, 1 H), 1.50 (m, 1 H), 1.35 (d, J = 7.2 Hz, 3 H), 1.14 (m, 1 H); ES' MS: 459 (M+l).
Example 2-67:
(4S,12aS)-l-Cyclobutyl-N-f(4-fluorophenyl)methyll-7-hyd roxy'4'methyl-6,8dioxo' 1,2,3

,4,6,8,12,12a-octahvdropvrido[r,2':4,5lpyra?,ino[l,2-a]pvrimidine-9-carboxamide.

a) ((3S)-3-Aminobutyljcyclobutylamine bishydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl
228

((IS)-l-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmoi) and cyclobutylamine (0.05 mL, 0.609 mmol) was prepared [(3S)-3'Aminobutyl]cyclobutylamine bis-hydrochloride in two steps (23 rag, 27%). iH NMR (methanol-oVCDCla) 5 8.86 (s, < 1 H), 7.97 (s, < 1 H), 3.46 (m, 1 H), 3.21 (m, 1 H), 2.74 (m, 2 H), 2.14-2.08 (m, 4 H), 1.94-1.62 (m, 5 H), 1.13 (d, b)
(4S,12aS)-l-CyclobutyJ-N-((4-fluorophenyl)methyl)-7-hydroxy-4-methyl-6,8-di oxo-l,213,4,6l8,12,12a-octahydropyrido[l',2'4,5]pyrazino[l,2-a]pyrimidine-9-carboxam ide. In a similar manner to that described in example Z*35a, from 16 (18 mg, 0.39 mmol) and [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride (23 mg, 0.107 mmol),
(4S,12aS)-l-cyclobutyl-N-[(4-fluorophenyl)methyl]-4-methyl-6,8-dioxo-7-l(phenylmeth yl)oxy]-l,2,3,4,618,12112a-octahydropyrido[r,2'-'4,5]pyrazino[l,2-a]pyrimidine-9-carbox amide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid after purification by HPLC (4.5 mg, 25 % 2 steps). !H NMR (CDC13) 8 12.54 (s, 1 H), 10.48 (s, 1 H), 8.20 (s, 1 H). 7.31 (m, 2 H), 6.98 (m, 2 H), 5.02 (m, 1 H), 4.61-4.57 (m, 2 H), 4.26-4.14 (m, 3 H), 3.05 (m, 1 H), 2.90 (m, 1 H), 2.49 (m, 1 H), 2.12 (m, 1 H), 2.05-1.87 (m, 3 H), 1.84-1.61 (m, 3 H), 1.46 (m, 1 H), 1.32 (m, 3 H); ES+ MS: 455 (M+l).
Example Z-68:
229

(4S,12aS)-N-f(4-Fluorophenvl)mel:hvl|-7-hvdroxv4-methv1-l-(2-met.hvlpropyl)-6,8-diQx o-l,2,3.4,6,8,12,12a-octahvdropvridofr.2'-4,5lpvra2ino[l,2-a1pvrimidine-9-carboxamid e

a) ((3S)-3-Aminobutyl](2-methylpropyl)amine bis-hydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from
1,1-dimethylethyl [(IS)-l-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and (2-methylpropyl)amine (0.06 mL, 0.609 mmol) in two steps as the bis-hydrochloride salt (22 mg. 25 %). "H NMR (methanol-rfi/CDCla) 5 3.25 (br s, 1 Il), 2.91 (br s, 2 H), 2.64 (m, 2 H), 2.02-1.93 (in, 3 H), 1.17 (m, 3 H), 0.88 (m, 6 H).
b)
(4S,12aS)-N-((4-Fluorophenyl)methyl]'7-hydroxy4-methyl-l-(2-methylpropyl) -6,8"dioxo-l,2,3,4,6,8,]2,12a-octahydropyrido[l\2M,5.]pyrazino[l,2-a]pyrimidine-9-car boxamide. In a similar manner to that described in example Z-35, from 16 (16 mg, 0.035 mmol) and [(3S)-3Aminobutyl](2-methylpropyl)amine bis-hydrochloride (20 mg, 0.0925 mmol),
(4S,12aS)-N-{(4-f]uorophenyl)methyl]-4-methyl-l-(2-methylpropyl)-6,8-dioxo-7-l(pheny lmethyDoxy]-1,2,3,4,6,8,12,12a-octahyd ropyrido[r,2':4,5]pyra7,ino[l,2-ajpyrimidine'9-
230

carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (13 mg, 68% 2 steps). 'H NMR (CDCla) 6 12.57 (s, I H), 10.46 (s, 1 H), 8.27 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 4.98 (m, 1 H), 4.63-4,54 (m, 2 IT), 4.45 (m, 1 H),4.26-4.16 (m, 2 H), 2,91 (m, 1 H), 2:77nr, 1 H), 2.24 (m, 1 H), 2.14-2.03 (m. 2 H), 1.63 (m, 1 H), 1.48 (m, 1 H), 1.33 (in, 3 H), 1.09 (m, 1 H), 0.850 (m. 3 H), 0.789 (m, 3 H); ES+MS:457(M+1).
Example Z-69:
(4S.12aS)-N-f(4-Pluorophenvl)methvl]-7-hvdroxvl.4-dimethvl-6.8-dioxo-1.2,3,4.6.8.12 .12a-octahvdropvridolr,2':4.5]pvrazino[],2-a]pvx,imidine-9-carboxamide.

a) {(3S)-3-Aminobutyl]methy]amine bishydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from 1,1-dimethylethyl [(IS)-.l-methy]-3"oxopropyl]carbamate (76 mg, 0.409 mmol) and excess methylamine (2 M in tetrhydrofuran) in two steps as the bis hydrochloride salt (17% 2 steps). 'H NMR (methanol-aVCDCb) 6 3.16 (m, 1 H), 3.08 (s, 2 H), 2.83 (m, 2 H), 2.45 (s, 3 H), 1.88 (m, 1 H), 1.75 (m, 3. H), 1.09 (m, 3 H).
231

b) .
(4S,12aS)-N-f(4-F]uoropheny])methy].|-7-hydi'Oxy-l,4-dimethyl-6,8-dioxo-1,2,3s 4,6,8,12,12a_octahydropyrido[r,2':4,5]pyrazino[l,2'a]pyi'imidine-9'carboxainide. In a similar manner to that described in example Z-35, from 16 (18 mg, 0.0398 mmol) and [(3S)-3-aminobutyl]methylarnine bis-hydrochloride (19 mg, 0.109 mmol,
(4S,12aS)-N-[(4fluorophenyl)methyl)-l,4-dimethyl-618-dioxo-7-[(phenylmethyl)oxy]-l, 2,3,4,6,8,12,12a-octahydropyrido[l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (7 mg, 44% 2 steps). >H NMR (CDCla) 6 12.53 (s, 1 H), 10.47 (s, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 5.04 (1 H), 4.60 (m, 2 H), 4.23 (s, 3 H), 2.83-2.80 (m, 2 H), 2.32 (s, 3 H). 2.13 (m, 1 H), 1.48 (m, 1 H), 1.34 (m, 3 H); ES- MS: 415 (M+l).
Example Z-7Q:
(46,.12a6)-iV-f(4-Fluorophenvl)methvn-7-hvd roxv4'methyl"6,8'dioxo'l'(tetrahvdro'2N •thiopvran-4-vl)-1.2,3,4.6.8.12,12a-octahvdropvridofl',2'-'4,5]uvrazino[3,2v<]pvriinidine

The title compound wae made in two steps using a similar process to that described in example Z-2. 16 (25 mg, 0.055 mmol) and free based

[(3£)-3-aminobutyl]tetrahydro-2/f-tluopyran-4-ylamine (48 mg, 0.26 mmol) were
232

reacted in dichloromethane (2 ml,) with acetic acid to give
(46,,12a6)-Ar-[(4-fluorophenyl)methyl]-4-methy]-6,8-dioxo-7-[(phenylmethyl)oxy]-l-(tet
rahydro-2i/-thiopyran-4-y])-1,2,3,4,6,8,12,12a-octahydropyrido[]',2':4,5]pyi'azino[l,2-,3
]pyrimidine-9-carboxamide (16 mg, 49%) as a film. This material was debenzylated
in a second step in a manner similar to Z26 to give
(4S',12a-A[(4-fluorophenyl)methyl]-7-hydroxy4-methyl-6,8-dioxo-l-(tetrahydro-2Ar-
thiopyran-4-y])-l.,2,3,4,6,8,12, a-octahydropyridoU'.SjpyrazinoU-.dpyrimidine-
g-carboxamide (8 mg, 59%) as an off-white solid. 'H NMR (400 MHz, CDC13) 8 1.30
(d, J= 7.2 Hz, 3H), 1.53-1.58 (m, 1H), 1.72-2.10 (m, 5H), 2.56-2.76 (m, 5H), 2.84-2.87
(m, 2H), 4,18 (dd, J= 2.8, 14.0 Hz, 1H), 4.26 (dd, /= 3.4, 14.2 Hz, 1H), 4.92-4.97 (m,
1H), 6.96-7.00 (m, 2H), 7.29-7.36 (in, 2H), 8.31 (s, 1H), 10.48 (m, 1H), 12.48 (br, 1H);
ES MS: 501 (M+l).
Example Z-7.1.:
(45.12a>S!)-N-K2,4-DifluoroDhenvl)methv)]-7-hvdroxvl.4-dimethvl-6.8-dioxo-1.2.3.4.6.8
.12,12a-octahvdropvri.dofr.2':4.5lpvrazino|.l,2-fl.]pvrimidine-9 carboxamide.

a) [(35)-3-Aminobutyl]methylamine dihydrochloride was prepared in a similar
manner as described in example Z-47. 'H NMR (400 MHz, CDC13) 6 1.18 (d, J~ 6.8
Hz, 3H), 1.82-1.91 (m, 1H), 1.94-2.03 (m, 1.H), 2.53 (s, 3H), 2.89-2.93 (m, 2H),
3.22-3.30 (m. 1H), 8.02 (br, <1H), 8.81 (br, <1H).
233

b)
(45,J12aS)-N-[(2,4-Difluorophenyl)methy]]-7-hydroxy-l14-dimethyl-6l8-dioxo-l,2,3,4,6,8
,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-fl]pyrimidine-9-carboxamide, The title
compound was made in two steps using a similar process to that described in example
Z-2. 16a (40 mg, 0.085 mmol) and free based [(35)-3-aminobutyl]methylamine (24
mg, 0.23 mmol) were reacted in dichloromethane (2 raL) with acetic acid to give
(46',12a!l-N-[(214-difluorophenyl)methyl]'l,4-dimethyl-6,8-dioxo-7-l(phenylmethyl)oxy
]-l,2,3,4,6,8,12,12a-octahydropyrido[l\2':4,5]pyrazino[l,2-tfJpyrimidine-9-carboxamide
(39 mg, 89%) as a film. This material was hydrogenated in a second step as
described in example Z"2 to give
(4iS',12a6)-AfK2,4-difluorophenyl)methyl]-7-hydvoxy-l,4-dimethyl-6,8-dioxo-1,2,3,4,6,8
,12,12a-octahydropyridolr,2':4,5]pyrazino[l,2v)]pyrimidine-9'carboxamide (32 mg,
97%) as an off-white solid. H NMR (400 MHz, CDC13) 6 1.33 (d, J= 6,4 Hz, 3H),
1.46-1.50 (m, 1H), 2.12-2.14 (m, 1H), 2.32 (s, 3H), 2.83 (m, 2H), 4.24 (m, 3H), 4.62 (m,
2H), 5.02 (m, Hi), 6.77-6.79 (m, 2H), 7.33 (m, 1H), 8.30 (s, 1H), 10.43 (s, 1H), 12,50 (br,
1H); ESJ MS: 433 (M+l).
Example Z-72-"
(45',12a6)-Ar-[(4-Fluorophenvl)methvll-7-hvdroxv-4-methvl-l-(l-methvlethvl)-6,8-dioxo
-l,2,3,4,6,8,12,12a-octahvdropvrido[r,2':4,5luvrazinofl,2-a]i3vrimidine-9-carboxamide.
234

The title compound was made in two steps using a similar process to that
described in example Z-2, 16 (27 mg, 0.060 mmol) and free based
[(3S)-3-aminobutyl](rmethylethyl)amine (67 mg, 0.51 mmol) were reacted in
dichloromethane (2 raL) with acetic acid to give
(4S, 12a6)-N-[(4-fluorophenyl)methyl3-4-methyM-(l-methylethy])-f),8-dioxo-7- [(phenyl
methyl)oxy]-l,2,.3,4,6,8,12,12a-octahydropyi'ido[r,2':4,5]pyrazino[l,2-<'3)pyrimidine-9-c
arboxamide (.18 mg, 56%) as a film. This material was hydrogenated in a second step
as described in example Z-2 to give
(4S, 12a l.S-.e..la-octahydropyridolT'Jpyrazinoll-alpyrimidinG-O-carboxamide
(15 mg, >100%) as an off-white solid. >H NMR (400 MHz, CDC13) S 1.02 (d, /= 6.4
Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 1.32 (d, J= 6.8 Hz, 3H), 1.54-1.58 (m, 1H), 1.94-2.03
(m, 1H), 2.71-2.76 (m, 1H), 2.82-2.88 (m, 1H), 3.13-3.16 (m, Hi), 4.16-4.19 (m, 1H),
4.30-4,33 (m, 1H), 4.48 (m, 1H), 4.55-4.65 (m, 2H), 4.97-5.00 (m, 1H), 6.97-7.01 (m,
2H), 7.30-7.34 (m, 2l-l), 8.28 (s, 1H), 10.51 (m, 1H), 12.55 (s, 1H); ES+ MS: 443 (M+l).
Example Z-73:
(4iS',12a5)-Ar-[(4-Fluorophenvl)methvl3-7-hydroxy l,4--bis(2-methvlpropyl)-6,8-dioxo-1,2
.3.4,6.8.12,12a-octahydropyrido[r,2':4.5lpvrazino[l.2-alDvrimidine-9-carboxamide.
235

The title compound was made in two steps using a similar process to that described in
example Z-2. 16 (25 mg, 0.055 mmol) and free based
[(3S)-3-amino-5-methylhexyl](2-methyJpropyl)amine (21 mg, 0.11 mmol) were reacted
in dichloromethane (2 mL) with acetic acid to give
(4S, 12a6)-Ar-[(4-fluorophenyl)methyl]-J.,4-bis(2-methylpropyl)-6,8-dioxo-7-[(phenylmet
hyl)oxy]-l,2,3,4,618112,12a-octahydropyrido[r,2,:4,5.jpyrazino[.l,2v-7jpyrimidine-9-carbo
xamide (8 mg, 25%) as a film. This material was hydrogenated in a second step as
described in example Z-2 to give
(46',].2a)-A-[(4-fluorophenyl)methyl]-7-hydroxy-l,4-bi6(2-methylpropyl)-6,8dioxo-l121
3l4)6,8112,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-aJpyrimidine-i}-carboxamide (5
mg, 78%) as an off-white solid. »H NMR (400 MHz, CDC13) 6 0.74 (d, J= 6.4 Hz, 311),
0.84 (d, J = 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.66 (m, 5H), 1.75-1.82 (m, 1H),
2.05-2.09 (m, 2H), 2.21-2.26 (m, Hi), 2.72-2.79 (m, 1H), 2.87-2.93 (m, 1H), 4.16-4.26
(m, 2H), 4.38 (in, Hl), 4.55-4.66 (m, 2H), 4.93-4,99 (ra, 1H), 6.97-7.02 (m, 2H),
7,31-7.34 (m, 2H), 8.27 (s, 1H), 10.49 (m, 1H), 12.61. (s, 1H); ES+ MS: 499 (M+l).
Example ZZ-1 to ZZ-24
Examples in table below were isolated as a mixture of diastereomers ranging from
11 to >10:1 ratios of stereoisomers at the center indicated as undefined.
236

236

Characterization data reported herein consists of observed mass spectral signals for molecular ions (M+I) of the compounds using electrospray ionization methods in the positive mode using LC/MS techniques well known in the field. Reported retention times refer to observed UV peaks confirmed by NMR methods for the examples beJow using the following gradient on a phenomenex CJ8 reverse phase H.PLC column (150 mmX4.6 mm 5 micron). Solvent A = water w/ 0.1% formic acid, solvent B = acetonitrile w/ 0.1% formic acid. Gradient = 10%B for 1 min, gradient from 10% to 90% B from 1 to 9 min, ramping to 100% B at 9.01 min and holding at 100% B for 2 min. In several cases the diastereomers were not separable by the standard HPLC conditions reported above and thus reported as a single retention time.
237
[Table A]

238

239

The present invention further includes the following compounds.

[Table B]

No (R) m R»
1 4- F - CH.-J
2 4 -F -CH(CH3)2
3 4 - F - CH2CH3OCH3
4 2.4- F - CH;?
5 2 , 4 - F - CH(CH3)3
6 2 , 4 - F -CH3CH2OCH3
7 2 - F, 3 -C 1 - CH3
8 2 - F, 3 -C 1 -CH(CH3)2
9 i 2 - F , 3 - C 1 -CH2CH2OCH3
240

Experimental Example .1.
The HIV integrase inhibitory activity was investigated based on the following-assay method,
(I) Preparation of DNA solution
By the same method as that described in Experimental Example 1 of WO 2004/024693, a substrate DNA solution (2 pmol/yil) and a target DNA solution (5 pmol/ul) were prepared, After each target DNA solution was once boiled, a temperature was slowly lowered to anneal complementary chains, which was used. Each sequence of a substrate DNA and a target DNA is as described in the same Experimental Example.
(2) Measurement of inhibition rate (ICso value)
Streptavidin (manufactured by Vector Laboratories) was dissolved in a 0.1M carbonate buffer solution (composition: 90 mM NasCOa, 10 mil NaHCO-3) to a concentration of 40 yig/ml. Each 50 pi of this solution was added to a well of an immunoplate (manufactured by NUNC), this is allowed to stand at 4°C overnight to adsorb. Then, each well was washed with a phosphate buffer (composition: 13.7 mM NaCl, 0.27 mM KC1, 0.43 mM NaaHPO-i, 0.14 mM KH2PO.1) two times, and 300 pi of a phosphate buffer containing .1 % skim milk to block it for 30 minutes. Further, each well was washed with a phosphate buffer two times, 50 pi of a substrate DNA solution (2 pmol/pl) was added to adsorb at room temperature for 30 minutes while shaking, and this was washed with a phosphate buffer two times and, then, distilled water once.
Then, to each well prepared as described above were added 12 pi of a buffer (composition: 150 mM MOPS (pH7.2), 75 mM M11Cl2, 50 mM 2-mercaptoethanol, 25% glycerol, 500 pg/ml bovine serum albumin-fraction V), and 51 pi of a reaction solution prepared from 39 pi of distilled water. Then, 9 pi of an integrase solution (30 pmol) was added, and the mixture was mixed well. To a well as a negative control (NC) was added 9 pi of a diluting solution (composition: 20 mM MOPS (pH7.2), 400 mM potassium glutamete, 1 mM EDTA, 0.1% NP-40, 20% glycerol, 1 mM DTT, 4 M urea), and this was mixed well using a plate mixer.
After the plate was incubated at 30°C for 60 minutes, the reaction solution was discarded, followed by washing with 250 pi of a washing buffer (composition: 150 mM MOPS (pH7.2), 50 mM 2-mercaptoethanol, 25% glycerol, 500 pg/ml bovine serum albumin-fraction V) three times.
Then, to each well were added 12 pi of a buffer (composition: 150 mM MOPS
241

(pH7.2), 75 raM MgCb, 50 mM 2-mercaptoethanol. 25% glycerol, 500 pg/ml bovine serum albumin-fraction V), and 53 pi of a reaction solution prepared from 41 pi of distilled water. Further, 6 pi of a solution of a test compound in DMSO was added to each well, and 6 pi of DMSO was added to a well as a positive control (PC), followed by mixing well using a plate mixer. After the plate was incubated at 30°C for 30 minutes, I pi of a target DNA (5 pmol/pl) was added, and this was mixed well using a plate mixer.
After each plate was incubated at 30°C for 10 minutes, the reaction solution was discarded, followed by washing with a phosphate buffer two times. Then, an anti-digoxigenin antibody labeled with alkaline phosphatase (sheep Fab fragment:

manufactured by Boehringer) was diluted 2000-fold with an antibody diluting solution, 100 pi of the diluent was added to bind at 30°C for 1 hour, and this was washed successively with a phosphate buffer containing 0.05 % Tween20 two times, and a phosphate buffer once. Then, 150 pi of an alkaline phosphatase coloring buffer (composition: 10 mM paranitrophenyl phosphate (manufactured by Vector Laboratories), 5 mM MgCb, 100 mM NaCl, 100 mM TrisHCl (pH 9.5)) was added to react at 30°C for 2 hours, 50 pi of a IN NaOH solution was added to stop the reaction, an absorbance (OD405 nm) of each well was measured, and an inhibition rate (ICso) was obtained according to the following calculation equation.
Inhibition rate (%) = 100[]-{(C abs.- NC abs.) / (PC abs.- NC abs.)}]
C abs.; absorbance of well of compound
NC abs.: absorbance of NC
PC abs.: absorbance of PC
Results are shown below.
[Table I]

Example No.	Integrase inhibitory activity (IC50, ng/ml)
C-2	3.3
F-2	3.8
H-2	3.2

The present compound showed the strong integrase inhibitory activity against HIV.
Experimental Example 2
242

A derivative of 293T cells expressing an attachment factor to improve adherence to plastic were used for the assay. A VSV-g pseudotyped HIV vector that expresses luciferase (herein referred to as PHIV) was produced by transfection of cells with the pGJ3-Luci vector plasmid (Jarmy, G. et al., J. Medical Virology, 64:223-231, 2001) and pVSV-g (Clontech). Cells were mixed with the PHIV vector and then mixed with serially diluted compounds. After incubation at 37°C and 5% CO2 for two days, the plates were read by using Steady Glo luciferase assay reagent (Promega) as recommended by the manufacturer. To assess noirHIV specific inhibition, a similar assay was performed, except that cell/PHIV vector mixture was replaced by cells which had been previously transduced and constitutively expressed luciferase.
[Table 2]

Example number	PHIV IC50 *=<10 nM, **=10-100 nM, ***>100nM
Z-1	+
Z-2	*
Z-3	*
Z-4	*
2-5	*
Z-6	*
Z-7	+
Z-8	**
Z-9	*
Z-10	*
z-11	*
Z-12	*-
Z-13	**•
Z-14	**
Z-15	*
Z-16	*
Z-1 7	*
Z-18	*
Z-19	*
Z-20	**
Z-21	*
Z-22	*
Z-23	*

243

Z-24	*
Z-25	*
Z-26	*
Z-27	***
Z-28	*
Z-29	*
Z-30	*
Z-31	|
Z-32	*
Z-33	*
Z-34	*
Z-35	*
Z-36	*-
Z-37	*
Z-38	±*
Z-39	*
Z-40	-*

Z-41 *
Z-42 *
Z-43 *
Z-44 *
Z-45 *
Z-46 *
Z-47 *
Z-48 *
Z-49 *
Z-50 *
Z-51 *
Z-52 *
Z-53 *
Z-54 *
Z-55 +*
Z-59 *
Z-60 *
Formulation Example
A term "active ingredient" means the present compound, a tautomer thereof, a pharmaceutical acceptable thereof, or a solvate thereof.
(Formulation Example 1)
A hard gelatin capsule is prepared using the following ingredients-'
dose
(mg/capsule)
Active ingredient 250
Starch (dried) 200
Magnesium stearate 10
244

Total 460rag
(Formulation Example 2)
A tablet is prepared using- the following ingredients:
dose
(mg/tablet)
Active ingredient 250
Cellulose (microcrystalline) 400
Silicon dioxide (fumed) 10
Stearic acid 5
Total 665mg
Ingredients are mixed, and compressed to obtain tablets, each weighing 665 mg.
245

[Name of Document] Scope of Claims
1 . A compound of the formula
(wherein,
Zi is NR/<;
Il4 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO2. NRa (R is hydrogen or lower alkyl), _N= and =N-)), 0 or CH2;
Z2 is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from 0, S, SO, SO2, NRS (R5 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy or optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SOa. NR3 (R5 is selected independently from the same substituent group as R'O, "N= and N')), -N= or
246

=N-;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from O, S, SO, SOaand Nil, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally

substituted heterocycleoxy or optionally substituted amino.'
Ri and Z2part taken together forms a ring, where the compound (I) is represented by the following formula (I-I), or (I-II)•

(wherein,
A ring is optionally substituted heterocycle;

II1"1 and Rx are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO2. NR5 (Rn is selected independently from the same substituent group as R'O, -N= and =N"), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted
247

heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyL'
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, Rxis not present;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from 0, S, SO, SO2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;
R2 is optionally substituted aryL'
R;5 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)

(wherein,
D ring is optionally substituted heterocycle;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from 0, S, SO, SO2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino));
or a pharmaceutically acceptable salt, or solvate thereof.
2. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen.
3. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein X is lower alkylene! II2 is phenyl or phenyl substituted with at least halogen.
248

4. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
5. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R:i is hydrogen.
6. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen or lower alkyl; X is lower alkylene.' R2 is phenyl or phenyl substituted with at least halogen; R3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
7. A compound of the formula-

(wherein,
A ring is optionally substituted heterocycle.'
R1'1 and Rx are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substitttited phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO2, NRD (11° is selected independently from the same substituent group as R'O, -N= and =N_), hydroxy,

optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted
249

heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbojiyl or optionally substituted aminocarbonyl;
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, Rx is not present;
R1 is hydrogen or lower alkyl.'
X is a single bond, a heteroatom group selected from O, S, SO, SChand NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino);
or a pharmaceutically acceptable salt, or solvate thereof
8. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein R1 is hydrogen or lower alkyl; X is lower alkylene; R2 is phenyl or phenyl substituted with at least halogen; R;i is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.
9. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.

10. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein Rx is hydrogen.' R3'1 is hydrogen or optionally substituted lower alkyl.
11. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is an optionally substituted and optionally condensed 5- to 7-membered heterocycle containing 1 to 2 hetero atom(s).
(wherein,
A ring is an optionally substituted and optionally condensed 5" to 1- membered
250
12. A compound of the formula:

heterocycle containing 1 to 2 hefcero atom(s);
the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof!
R1'1 and Rx are independently .hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO2, NR5 (R5 is selected independently from the same substituent group as Il4), -N= and =N0, hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or
It1 is hydrogen or lower alkyl!
R is independently selected from halogen and Substituent group Sli
Substituent group SIC optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (wherein the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, O, S, SO, SO2, NR" (R" is hydrogen or lower alkyl), -N= and =N0, lower alkoxy lower alkyl, amino lower alkyl optionally
251

substituted with mono- or dr lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di- lower alkyl, optionally substituted lower alkyl sulfonyl amino, halogenated lower alkoxy, hydroxy lower alkyl)
m is an integer of 0 to 3);
or a pharmaceutical acceptable salt, or solvate thereof.
13. A compound according to Claim 12, pharmaceutical!/ acceptable salt, or solvate

thereof, wherein Rx and R1'1 are independently hydrogen or optionally substituted lower alkyl.
14. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein Rx and R1'4 are hydrogens.
15. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R3 is hydrogen.

16. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.
17. A compound according to Claim 7 or 12, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is any one of the followings:

(wherein, R20 to R'10 are each independently a group selected from Substituent group S2, or any two groups of R20 to R10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R20 and R22), (R23 and R2'0, (Rand R2<0, (R27 and R29), (Rand Ri), (R32 and IIO, (Rand R™), (R37and R™), and (R39andR'in), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.
Substituent group S2: hydrogen, optionally substituted lower alkyl, optionally
252

substituted cycloalkyj, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted arj'loxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyt; optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with Optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO2, NR5 (R5 is independently selected from the same Substituent group as R'O, "N= and =N_)
the stereochemistry of an asymmetric carbon represented by * shows R" or S-configuration, or a mixture thereof)
.18. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein R2" to R'10 are each independently hydrogen or substituted lower alkyl, or any two groups of R20 to R'10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3" to 7- membered heterocycle, or each combination of (lo and R22), (R and R2'0, (R™ and R2G), (R27and R*>), (Rand Rsi), (R32and R), (R3S and R™), (Rand R38), ancj (R39andR"»), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.
19. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-I); one of R20to R25 is optionally substituted lower alkyl and the others are hydrogens.
20. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-I); one of (II20 and R22), (R23 and It2,1), and (R25and R20'), taken together with the neighboring atom, may form an
253

optionally substituted 5' to 7- membered carbocyle or optionally substituted 5- to 7-membered heterocycle.
21. A cpmpound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-I); Z=NR26, and R25 and R26 taken

together with the neighboring atom may form an optionally substituted 5- to 7-membered heterocycle.
22. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of R27 to R30 is optionally substituted lower alkyl and the others are hydrogens.
23. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of (R27and R2U) and (R:!0 and R31), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.
24. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); Z=NR31, and R30 and R31 taken together with the neighboring atom may form an optionally substituted 5- to 7-membered heterocycle.
25. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of II32 to R3!Jis optionally substituted lower alkyl and the others are hydrogens.
26. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A'3); one of (R'32andR3'J),(R3;iandR3'5),(R37andR38),and(R30andR't0), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.
27. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate

thereof, wherein A ring is a ring represented by (A-3); Z=NR',(), and R39and R'K) taken together with the neighboring atom may form an optionally substituted 5" to 7-membered heterocycle.
28. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein Rx is hydrogen; R1'1 is hydrogen or optionally substituted lower; R3 is hydrogen.' m is 1 to 3 and at least one of Rs is halogen; A ring is a ring described in
254

Claim 17.
29. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein Rx is hydrogen; It1'1 is hydrogen; R3 is hydrogen," m is 0, or 1 to 3 and at least one of R is halogen; A ring is a ring described in Claim 17; R20 to R'f0 are each independently hydrogen or substituted lower alkyl, or any two groups of R20 to R*10, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3" to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R20 and R22), (R23 and R2'1), (R2rj and R2G), (R" and R29), (Rao and R31), (R32 and R3"), (R35 and R3(0, (R37 and R™), and (R3%ndR40), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5' to 7-membered heterocycle.
30. A compound of the formula:

(wherein,
D ring is optionally substituted heterocycle;
R1 is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from 0, S, SO, SO2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;
R2 is optionally substituted aryl;
R3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substitxited aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino);
or a pharmaceutically acceptable salt, or solvate thereof
31. A compound selected from the group consisting of:

(3i?,lla>-A/-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-tf]pyrido[l,2-fl']pyrazine-8-carboxamide;
255

(4a/e,13a6)-A';[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2l3,48,5,9,11,13,13a-octahydrolN-pyrido[l,2v2]pyrrolo[l',2'3,4]imidazo[l ,2-<3']pyra7,ine-8"carboxamide;
(3a6,,13a)-Ar-[(2,4-Difluorophenyl)methyl]-8-hydi-oxy-7,9-dioxo-l,2,3,3a,4,5,7,9,13113a-decahydropyridolr,2':4,53pyrazino(l,2-a]pyrrolo[l,2-dpyrimidine-10-carboxamide;
(4a5:i3aie)-7V-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4a,5,9,ll,13,13a-octahydro-li7-pyrido[l,2-a]pyri:olo[l',2':3,4]iinidazoll,2-a']pyrazine'8-carboxamide;
(4aS',13a)-Ar-[(4-Fluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4al5,9,ll,13,13a-octahydio-.lN:pyrido[l,2-a]pyrrolotr,2':3,4]imidazo[l,2(7l]5yrazine'8-carboxamide;
(35,1lla)-N-[(2,4-Difluoropheny])methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-213,5,7,ll,lla"hexahydro(l,3]oxazo]ol3,2-a]pyrido[l,2-rfipyrazine-8'carboxamide.'
(3a5; 13a6)-7V-((4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[l',2':4,5]pyrazino[l,2'a]pyrrolo[l,2-dpyrimidine-10-carboxamide.'
(3-S',lla/il)-A'r-[(2,4-Difluorophenyl)jnethyl]-6-hydroxy-3-[(l1S)-l-raethylpropyl]-517-dioxo 2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-]pyrido[.l,2'fl']pyrazine-8-carboxamide;
(35*,lla7?)-A-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-mGthyl-5,7-dioxo-2,3,5,7,n,lla-hexahydro[l,3joxazolo[3,2- (35,,lla/i)-N-[('l-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,G,7,ll,lla-he
256

xahydro[l,3]oxazolo[3,2-a]pyridon,2-(7']pyrazine-8-carboxamide;
(35,,lla7e)-A'-[(2l4-Difluorophenyl)methyl]-3-(l,l-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,1 la-hexahydro[l,3]oxazolol.3,2-a)pyrido[l,2-rflpyrazine-8-carboxaraide;
(3iS',llai9-3-(l,l-Dimethylethyl)-/V-[(4-fluorophenyl)methyl]-6-hydroxy-5l7-dioxo-2,315,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyridofl,2-<7r]pyrazine-8-carboxamide;
(35')nai2)-A':[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3)5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l]2"rf]pyraziiie-8-cauboxamide;
(36:ila72)-A[(2,4-Difluorophenyl)methy]]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,ll)llla-hexahydro[lJ3]oxazolo[3,2-a]pyrido[l,2- (26,,3)-/V-{(2,4-Difluorophenyl)methyl]-6-hyd roxy"3-methyl"5,7-dioxo*2*phenyl"2,3,5,7
,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-rf]p yrazine-8-carboxamideJ
(3lt, lla6)-A[(2,4-Difluoi'ophenyl)mGthyl]-6-hydi-oxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-]pyrido[l,2-fl']pyrazine-8-carboxaraide;
(3fl,lla)-/V-((2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-mGthylpropyl)-5,7-dioxo-2>3,5,7,ll,lla"hexahydro(l,3]oxazolo[3,2-a]pyrido[l,2-fl']pyrazine"8-carboxamide;
(5a/i, 14a/?)-/V-[(2,4-Difluorophenyl)methyl]-ll-hydroxy 10,1210X0-1,2,3,4,5a,6,10,12,14, Ma-decahydropyLidofl-Jpyridotr'limidazotl-pyrazine-O-carboxamide;
257

(25',34S)-Ar-[(2,4-Difluorophenyl)methyl]-G-hydroxy-3-[(me.thyloxy)methyl]-5,7-dioxo-2-phenyl*2,3,5,7,ll,lla-hexahydro[l,3]oxazolof3,2-a]pyrido[ll2-c/]pyi-azine-8-carboxamide
(35',l.la7i)-3-(Cyclohexylmethyl)-A/-[(2,4-difluoropheny])methyl]-6-hyd roxy5,7-dioxcr2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-rf]pymzine-8-carboxamide;
(3i9llla/5D-Ar-[(2,4-Difluorophenyl)methyl]-6-hydroxy3-(l-methylethyl)-5,7-dioxo-2,3,5,7,ll,lla-hexahydro[l,3joxazolo[3,2-a]pyridoll,2-rflpyraziHe-8-carboxamide;
(5a/?,14aiS)-A':[(2l4-Diflxiorophenyl)methyl]-12-hydroxyll,13-dioxo-5a,6a,7,ll,13,14a-hexahydro-5T-incieno[r,2':4,5][l,3]oxazolo[3,2-a]pyrido[l,2'a']pyrazine-10-carboxamid
ol

el
(2,,37e,lla)-A[.(2l4-Difluorophenyl)methyl]-6-hydroxy-5)7-dioxo-2l3-diphenyl-2,3,5,7,
11,1 la-hexahydro[l,3]oxazolo[3,2-a]pyrido[l,2-o']pyrazine-8-carboxamide;
(2£,,3i?,naid-7V-[(2,4-difluorophenyl)methyl]-6iiydroxy5)7-dioxo-2,3-dipheny]-2,3,5,7,
ll,lla-hexahydro[l)3]oxazolo[3,2-a]pyrido[l,2-a']pyi,azine-8-carboxamide;
(3,lla6)-/V-[(2,4-Difliiorophenyl)methyl]-6-hydroxy3-(l-methylethyl)-5,7-dioxo-2,3,5,
7,ll>lla-hexahydro[l,3]oxazolo[3,2-a]pyridofl,2-o']pyrazine-8-carboxamide;
(SS'.lla-yV--DifluorophenyDmethyU-e-hydroxyS--dnethylthethyll-S-dioxo-
2,3,5,7,11,] la-hexahydro[l,3]oxazolo[3,2-a]pyridoll,2-rf]pyrazinc-8-carboxamide;
258

(36',lla/£)-/vr-[(2,4-Difluoropheayl)raethylJ-6-hydroxy-3-[2-(metliylsulfonyl)ethyl]-5,7-di
oxo-2,315,7,ll,lla-hexahydro[l,3]oxazolo[3,2-a3pyrido[l,2-<7']pyrazine-8-carboxamide;
(36'1lla7d-A'-[(2,4-Difluorophenyl)methyl]-6-hydi'oxy-3-(li7-mdol-3-ylmGthyl)-5,7-dioxo
-2,3,5,7,ll,lla-hexahydro[l,3]oxazolo[3,2-]pyrido[l,2-tf]pyrazine-8-carboxainide;
(47?,12a/?)-iV-l(4-fluorophenyl)methyl]-7-hyd roxy-4-methyl-l-(2-methylpropyl)-6,8diox
0-1,2,3,4,6,8,12,12a-octahydropyrido[l', 2':4,5]pyrazino[l, 2-/3]pyrimidine-9-carboxa mid
(4i2,12a7?)-A[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyM-(l-met.hy]efchyl)-6,8-diox
o-1,2,3,4,6,8,12,12a'octahydropyrido[l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxamid
e;
(45',12a-7V-[(2)4-Difluoi-ophenyl)methyl]-7-hydroxy-4-methyl-.l-(2-methylpropyl)-6,8-
dioxo-1,2,3,4,6,8,12,12a-octahydi''opyridof 1',2':4,5]pyrazino[1,2]pyi-imidine-9-carboxa
midei
(46',12a6)-l-(Cyclopropylmethyl)-Ar-[(2,4-difluoi-ophGnyl)methy]]-7hydroxy-4-methy]-6
,8-dioxo-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-<7]pyrimidine-9-cai'bo
xamide;
(4U2a6)-7V-[(2,4-Difluorophenyl)methyl]-l-(2-furany]niethyl)-7-hydroxy-4-methyl-6,8
-dioxo-l,2,3,4,6,8,12,12a-octahydropyrido[l',2'-'4,5]pyrazino[l,2-a]pyrimidine-9-carbox
amide;
259

(46,,12a-5)-A-[(2,4-Difluorophenyl)methyl]-7-hyd roxy"4*inethyl'6,8"dioxcr l-(l,3"thiazol-
2-ylmethyl)-1,2,3,4,6,8,12,12a-octabydropyridofl\2M,5]pyrazino[l,2v;]pyrimidme-9-c
arboxamidei
(4a7i,6a,.l4a6)-Ar-[(2,4-DifluoropRenyl)methyl]-12-hydroxy-ll,13-dioxol,3,4,4a,5,6a,
7,11,13,14a_decahydro-2./7-pyrido[r,2':4,5]pyrazmo[ll2-a][3, ljbenzoxazine- 10"carboxa
mideJ
(4-a72,6al4a)-AtK4-Fhiorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,G,6a,7,11
, 13,14a'decabydro-2i7-pyrido[r,2'4,5]pyrazino[l,2-a][3,l]beazoxazinel0-carboxamide
(36',4a,6ai?,14a)-/V:[(2,4-Difluorophenyl)methyl]l2-hydroxy-ll,13-dioxo-3-phenyl-]
,3,4,4a,5,6a,7,1.1,13,14a-decahydro-2N-pyrido[l',2,:4,5]pyrazino[l,2-a][3,l]benzoxazine
- 10'carboxamide,'
(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-raethylpropyl)-ll,13-d
ioxo-1,2,3,4,4a,5,6,6a,7, ll,13,14a-dodecahydropyrido[r,2'-'415]pyrazino[l,2a]quinazoli
ne-10-carboxamide;
(GaR,7aS,llaS)-N-[(214-Difluorophenyl)methy]]-l-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,
ll,lla,13-decahydro-6H-pyi'idoU\2':4,5]pyrazino[l,2-a]benzimidazole-3-carboxamide;
(6aS,7aS,llaS)-N-[(2,4-Diflviorophenyl)methyl]-l-hydroxy2,13-dioxo-2,6a,7,7a,8,9,10,
11,] la,13-decahydro-6H-pyi'idotl',2':4,5]pyrazino[l,2'a)benzimidazole-3-carboxamide;
260

(5aS)14aS)-N-[(2,4-Difluorophenyl)methyl]-ll-hydroxylO,12-dioxo-l,2,3,4,5a,6,10,12,
14)14a-decahydropyrido[l,2-a]pyrido[r,2':3,4]imidaxo[l,2-d]pyrazine-9-carboxamide;
(4a'll,14aR)-N-((2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,
14a-decahydro' 1.H-pyi'idoll,2c]pyi'ido[l',2':4,5]pyrazino[l,2-a]pyi'imidine-ll-carboxam
idei
(4/A12a)-A[(2,4-Difluoropheny])methyl]-7-hydroxy-4-methyl-l-(3-methylbutyl)-6,S-d
ioxol,2,3,4,6,8,12,12a-octahydropyrido[]',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxa
raideJ
(45'112a,S)-A'-K2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-l-(l-methylethyl)-6,8-di
OXQ-1,2,3,4,6,8,12,12a-octahydropyridotr', 5] pyrazinot 1,2-a]pyrimidine_9carboxam
ide;
(4£',12a£)-At[(2,4-Difluorophenyl)methyl]-7-hydroxy4-raethyl-l-(3-methylbutyl)-6,8-d
ioxo-l,2,3,4,6,8,12,.12a-octahydropyridolr,2':4,5]pyrazino[l,2-a3pyrimidine-9-carboxa
mide;
(45,,12a6)-7V-[(2,4-Difluoi-ophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-l-(3-pyridiiiyl
raethyl)-l,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazino[l,2-]pyrimidine-9-carbo
xamidei
(46U2a-l-Cyclopropyl-jV-((2,4-difluorophenyl)methyl]-7-hydroxy4-methyl-6,8-dioxo-
261

1,2,3,4,6,8,12,12a-octahydropyrido[r, 2'4,5]pyrazino[l,2-i9]pyrin'iidine-.9-carboxamide;
(46;i2a)-Al(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyM-f2-(methyloxy)ethylJ-
6,8-dioxo-]..2,3,4,6,8,12,12a-octahydropyrido[r,2'-4,5]pyrazino[l,2-a]pyrimidine-9-carb
oxamideJ
(3aS,5aS,13aS)-N-[(2,4-Difluoropheny])methyl]-ll-hydroxy-5-(2-methylpropyl)-10,12-d
ioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydi-o-lH-cyciopenta[e]pyrido[r,2'4,5]pyrazino[l,2
-aJpyi"imidine-9-carboxamide;
(SA'JlaA-to-DifluorophenyOmethylJ-S-ethyl-Ghydroxy-S.y-dioxo.S.y.ll.lla-h
exahydro[l,3joxa2olo[3,2-a]pyridoll,2-<3'jp3'razine-8-carboxamide.'
{4aS,6aS,14aS)-N-((2,4-Difluorophenyl)methyl]-12-hydroxy-6-f2-(4-morpholinyl)ethylj-
ll.,13-dioxo-l,2,3,4,4a,5,6,6a17,ll>13,14a-dodecahydropyrido[r,2':4,5]pyrazino(l,2-a]q
uina/.oline-10-carboxamide;
(3aR,5a.R,13aS)-N-[(2,4-DifJuoropheny])methyl]-ll-hydroxy-10,1210X0-1,2,3,38,4,53,
6,10,12, ISadecahydrocyclopentafdJpyridofl'.Sjpyrazino, l-b][l,3]oxazine-9-carbo
xamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methylJ-12-hydroxy-6-methyl-ll,13-dioxo-l,2,3
,4,4a, 5,6,6a, 7,1 J, 13,14a-dodecahydropyrido(r,2':4,5]pyrazino[l,2'ajquinazoline-10"car
boxamideJ
(4aS,6aS,14aS)-N-[(2,4-Difluovophenyl)methyl]-12-hydroxy6-[2-(methyloxy)ethylJ-ll,
262

13-dioxo-l,2,3,4,4a,5,6,6a,7,ll113,14a-dodecahydropyrido(r,2,:415]pyrazino[l,2-a]quin
azoline- 10-carboxamide;
(4aS,6aS,J4aS)-G-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxyl
l,13-dioxo-l,2,3,4,4a,5,6,6a,71ll,13,14a-dodecahydropyrido[.l',2,-"4)5]pyrazino[l,2-a]qui
nazoline- 10'carboxamide;
(3S, 11a. Jd- A-DifluorophenyDmethyU-S-ethyl-e-hydroxy-S.T-dioxo, 3,5,7, ll,lla-h
exahydro(.l,3.1oxazolo[3,2-a]pyi-ido(l,2-fl']pyrazine-8-carboxamide;
(36:ila)-3-Butyl-iV-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,ll,lla-h
• exahydro[.l,3]oxazolot3,2-a]pyi-ido[l,2-£7']pyrazine-8-carboxamide;
(36,,lla/i)-7V:[(2)4-Difluorophenyl)methyl]-6-hydroxy3-[(4-hydroxyphenyl)methyl]-5,7-
dioxo-2,3l5,7,ll,llaiiexahydro[l,3]oxazolo[3,2-aJpyrido[l,2-a']pyrazine-8-carboxamide
(4S,12aS)-.l-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-.l
,2,3,4,6,8,12,12a-octahydropyrido[r,2':4,5]pyrazinoll,2-a]pyrimidine-9-carboxamide;
(45,,12a5)-Ar-[(2,4-Difluorophenyl)inethyl]-7-hydroxy-4-methyl-6,8-dioxo-l-(tetrahydro-
2i/-thiopyran-4-yl)-l,2,3,4,6,8,12,].2a-octahydropyrido[.l,,2':4,5]pyrazino[l,2vi]pyriinid
ine-9-carboxamide;
(4£,,12a5)-7V-[(2,4-Difluoi-ophenyl)methyl]-7-hydroxyl,4-bis(2-methylpi-opyl)-6,8-dioxo
•l,2,3,4,6,8,.l2,12a-octahydi'opyi'ido(r,2':4,5]pyrazino[l,2-]pyrimidine-9'carboxamide;
263

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-ll)13-d
ioxo-l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[r,2':4,5]pyraziiio[l,2-a]quinazoli
ne'10-carboxamide."
(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-ll,13-dioxo-
l,2,3,4,4a,5,6,6a,7,ll,13,14a-dodecahydropyrido[l\2'-"4,5]pyrazino[l,2a]quinazoline-l
O'carboxamidei'
(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-ll,13-dioxo-6-[2-(l-pyrroli
dinyl)ethyl]-l,213,4,4aJ5,6,6a,7,ll,13,14a-dodecahydropyrido[l,,2':4,5]pyrazino[l,2-a]q
uinazoline-lO'carboxamidel
(4aS,14aS)-N-l(2,4-Difluorophenyl)methylJ-9-hydroxy8,10-dioxo-2,3,4,4a,5,6,8,10,14,l
4a-decahydro-lH-pyrido[l,2-c]pyrido[l'l2':4,5]pyrazino[l,2-a]pyrimidine-ll-carboxami
del
(4S>12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-raethyl-l-(2-(methyloxy)ethyl]-6,8-
dioxo-1,2,3,4,6,8,12,12a-octahydropyrido['l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carboxa
mide.'
(4S,1.2aS)-l-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-l,2,3
,4,6,8,12,12a-octahydropyrido[l',2':4,5]pyrazino[l,2'a]pyriiriidine-9-carboxamide;
264

(4S,12aS)-N-[(4-F]uorophenyl)methyl]-7-hydroxy4-methyl-l-(2-inethylpropyl)-6J8-diox
o-l)2,3,416,8,12,12a-octahydropyrido[l',2'-'4,5]pyi'azino[l,2-a]pyrimidine-9-carboxarnid
e;
(4S, 12aS)'N"[(4'Fluorop henyl)methyl]-7-hydroxy-l,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12
, 12a-octahydropyrido[l\2':4,5]pyrazmo[l,2-a]pyrirnidine-9-carboxamide;
(46Y,12a6)A-((4-Fluorophenyl)niethyl]-7-hydroxy-4-methyl-6,8-dioxo-l-(tetrahydi-o-2N
-thiopyran-4-yl)-l,2,3,4,6)8,12,12a'Octahydropyridoll',2':4,5jpyrazino[l)2a]pyrimidiae
-9-carboxamide;
(46:12a>-N-t(2,4-Difluorophenyl)methyl]-7-hydroxy-l,4-dimethyl-6,8-dioxo-1,2,3,4,6,8
,12,12aoctahydi'opyrido[]',2'-'4,5]pyiazino[l,2"a]pyrimidine-9"carboxainide;
(45;i2a6)-iV-[(4-Fluorophenyl)methyl]-7-hydroxy'4-methyM-(l-methylethyl)-6,8-dioxo
• 1,2,3,4,6,8,12,12a-octahydropyrido[].',2':4,53pyra zinof l,2-a]pyrimidine-9_carboxamide,'
(4£',12a6)-Al(4-Fluorophenyl)methyl]-7-hydroxy-l,4-bis(2-methylpropyl)-6,8-dioxo-l,2
,3,4,6,8,12,12a-octahydropyrido[].'12':4,5]pyrazinoll,2-a]pyrimidine-9-cai*boxamidei"
enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof;
mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers
thereof; and pharmaceutical acceptable salts thereof.
265

32. A compound selected from the group consisting of-'
(4a6',13a./?)-Ar-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,ll-dioxo-2,3,4a,5J9,ll,13,13a
-octahydro-lipyrido[l,2'a]pyrrolo[r,2':3,4]imidazo[l,2-fi(']pyrazine-8-carboxamide;
(4a iff, 13a.Ji)- A[(4-Fluorop henyDmethylj-lO-hydroxy-O.ll-dioxoa.S.O.ll.ISJSaoct
ah3'dro-lN:pyndo[].,2-a]pyrro]o[l')2'-"3,4]imidazo[l,2-a']pyrazine-8-cai-boxamide;
Olla-A'-DifluorophenyDmethylJ-e-hydroxy-S-Kli-l-methylpropyn-rj.T-dioxo
-2,3)517)ll,lla"hexahydro[l,3joxazolo[3,2-r2]pyrido[l,2-a']pyrazine-8-carboxamide;
(Slla-A--DifluorophenyDmethylJ-e-hydroxy-S-methyl-S.V-dioxo.S.S.V.ll.lla
-hexahydioll,3]oxazolo[3,2-]pyrido[l,2-c(']pyrazine-8-carboxamide;
{3S,,lla/f)-7V-l(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,ll,lla-he
xahydro[l,3]oxazolo[3,2-,9]pyrido[l,2-a']pyrazine-8'carboxamide;
(46'112a6)-Ar-[(2,4-Difluoropheny})methyl]-7-hydi'oxy4-methyM-(2-methylpropyl)-6,8-
dioxo-1,2,3,4,6,8,12,].2a-octahydi'opyrido[r,2':4,5]pyrazino[l,2'a]pyrimidine'9-carboxa
mide;
(46',12ag>-l-(Cyclopropylmetliyl)-7V1[(2>4-difluorophenyl)methyl]-7-hyclioxy'4-methyl-6
,8'dioxo-l,2,3,4,6,8)12,12a-octahydropyrido(l',2':4,5]pyrazino[l,2-a]pyrimidine-9-carbo
xamide;
(4ai2,6a/e,14a6)-Ar-[(2,4-Difluorophenyl)methyl]-12-hydroxy-l.l,13-dioxo-l,3,4,4a,5,6a,
7,11,13,.14a-decahydro-2jY-pyrido[r,2'-4,5]pyrazino[l12v:;][3,l]benzoxazine-10-carboxa
266

mide;
(4ai?,6a,14a-S)-N-[(4-Fluoi-ophenyl)methyl]-12-hydroxy-ll,13-dioxo- 1,3,4,4a, 5,6a,7.11
,13,14a-decahydro-2r-pyrido[l',2':4,5jpyrazino[l,2-a][3)l]benzoxazine-10-carboxamide
4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-l-oxa-4a,
8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide J
4R,9aS)-5-Hydroxy-4-methyl-6,lQ-dioxo-3,4,6,9,9a,10-liexahydro-2H-l-oxa-4a,
8a-diaza-anthracene-7-cai-boxylic acid 2,4,-difluoro-benylamide,"
2R,9aS)-5-Hydroxy-2-methyl-6,10dioxo-3,4,6,9,9a,10-hexahydro-2H-l-oxa-4a,
8a-diaza"anthracene"7-carboxylic acid 4-fiuorobenylamide.'
enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof;
mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers
thereof; and pharmaceutical acceptable salts thereof.
33. A compound according to claims 31 or 32 wherein the pharmaceutical
acceptable salt is a sodium salt.
34. A pharmaceutical composition comprising a compound according to any one of
Claims 1 to 33, or a pharmaceutical acceptable salt, or solvate thereof.
35. A pharmaceutical composition according to Claim 34, which is an anti'HIV
agent.
36. A process for the preparation of a compound of formula (I"20a)
267

wherein Rc is one or two halogen; R7- is Ci-aalkyl, Cc-narylCi-salkyl, Cei-iaryl, or
alkoxy; and P1 is Cc l-iarylCioalkyl;
comprising' condensing a compound of the formula

wherein R° is one or two halogen; Rs0 is Cisalkyl; and P1 is Ce-i-iarylCi-salkyli"
with a compound of the formula -

wherein Rz is Ci-salkyl, CG-uarylCi-salkyl, Cc-naryl, or alkoxy;
to form a compound of formula (I-20a).
37. A process for the preparation of a compound of formula (I-20b)

wherein R alkoxy; and P1 is Cfii-iarylCisalkyl;
comprising condensing a compound of the formula
268

wherein Rc is one or two halogen,' R50 is Ci-aalkylj and P1 is Cc-i-jarylCi-ealkyl;
with a compound of the formula

wherein R'- is Ci-aalkyl, Cc-MarylCi-salkyl, Csuaryl, or alkoxy!
to form a compound of formula (I-20b).
38. A process for the preparation of a compound of formula (I-21a)

wherein Re is one or two halogen; and P1 is Cc-i comprising condensing a compound of the formula

wherein Re is one or two halogen; R50 is Ci ealkyl; and P1 is Ceo-iarylCi salkyl;
with a compound of the formula

to form a compound of formula (I-21a).
269

39. A process for the preparation of a compound of formula (I-21b)

wherein R° is one or two halogen; and P1 is Coi'iarylCisalkyl;
comprising' condensing a coznpound of the formula

wherein Re is one or two halogen.' R50 is Ci-salkyl. and P1 is Ce-MarylCi salkyl;
with a compound of the formula

to form a compound of formula (1-2 Ib).
40. A process for the preparation of a compound of formula (I-22a)

wherein R° is one or two halogen; and P1 is Ce-HarylCi-»alkyl.'
comprising condensing a compound of the formula-
270

wherein R° is one or two halogen,' R50 is Ci-salkyl; and P1 is CGiiarylCi-salkyl.*
with a compound of the formula

to form a compound of formula (I-22a).
41. A process for the preparation of a compound of formula (I-22b)

wherein R° is one or two halogen; and P1 is Ce-i-iarylCi-salkyl;
comprising condensing a compound of the formula

wherein R° is one or two halogen! R50 is Ci-aalkyl; and P1 is Cc-MarylCi-salkyl;
with a compound of the formula

to form a compound of formula (I-22b).
42. A process for the preparation of a compound of formula (I-23a)

42. A process for the preparation of a compound of formula (I-23a)
271

wherein Re is one or two halogen.' and P1 is Cei'iarylCi-salkyl;
comprising condensing a compound of the formula

wherein Re is one or two halogen,' Rr,° is Ci-salkyL" and P1 is Cc-i-iarylCi-salkyl,"
with a compound of the formula

to form a compound of formula (I"23a).
43. A process for the preparation of a compound of formula (J-23b)

wherein Rc is one or two halogen; and P1 is CG-narylCi-aalkyli
comprising condensing a compound of the formula

wherein Re is one or two halogen; R50 is Cisalkyl; and P1 is CcM.iarylCi salkyl;
with a compound of the formula -
272

to form a compound of formula (I-23b).
44. A process for the preparation of a compound of formula (P24a)

wherein R° is one or two halogen; R/-1 is hydrogen, Cy-ccycloalkyl, heterocycle, or Ci-salkyl optionally substituted with hydroxy, C3 ccycloalkj'l, alkoxy, heteroc3'cle, heteroaryl, Cc-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-Salkyl or Ci-8alkyK
and P1 is CG-i-iarylCi-aalkyl;
comprising condensing a compound of the formula

wherein R€ is one or two halogen; Rn0 is Ci-salkyl; and P>- is CcHarylCi-aalkyl;
with a compound of the formula

wherein Rz is Ci-aalkyL" R/J is hydrogen, C3 ecycloalkyl, , heterocycle, or Ci-salkyl optionally substituted with hydroxy, Ca-ficycloalk}'l, alkoxy, heterocycle, heteroaiyl, Cfi-naryl, or amino, wherein said amino may be optionally substituted with -C(0)C)Balkylor Cisalkyl;
to form a compound of the formula (I-24a).
273

45. A process for the preparation of a compound of formula (I_24b)

wherein Rc is one or two halogen; R'-' is hydrogen, Cri-ncycloalkyl, heterocycle, or Ci-salkyl optionally substituted _ with hydroxy, C3-ccycloalkyl, alkoxy, heterocycle, heteroaryl, Cc-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-aalkyl or Cj-salkyl;
and P1 is Cc-HarylCi-salkyl."
comprising condensing a compound of the formula

wherein R° is one or two halogen,' RMI is Ci flalkyli and P1 is CG MarylCi-salkyl;
with a compound of the formula

wherein R"* is Ci-salkyl.' Rzl is hydrogen, C;icycloalkyl, heterocycle, or Ci-aalkyl optionally substituted with hydroxy, Cs-ocycloalkyl, alkoxy, heterocycle, heteroaryl, CriMaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-8alkyl or Ci-galkyl;
to form a compound of the formula (I-24b).
274
46. A process for the preparation of a racemic compound of formula (1-25)

wherein RG is one or two halogen; Rzl is hydrogen, C;i<;cycloalkyl, heterocycle, or Ci-salkyl optionally substituted with hydroxy, Cu-tjcycloalkyl, alkoxy, heterocycle, heteroaryl, Co-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ciaalkyl or Ci-salkyl; and P1 is Co-narylCi-salkyli'
wherein Re is one or two halogen; R50 is Ci-aalkyl; and P1 is Cc-MarylCi-salkyl;
with a racemic compound of the formula
comprising condensing a compound of the formula

wherein Rz! is hydrogen, Ca-ecycloalkyl, heterocycle, or Ci-salkyl optionally substituted with hydroxy, Cs-scycloalkyl, alkoxy, heterocycle, heteroaryl, Co-naryl, or amino, wherein said amino may be optionally substituted with - C(0)Ci-salkyl or Ci-salkyl;
to form a racemic compound of the formula (1-26).
47. A process for the preparation of a racemic compound of formula (I-26)

wherein R° is one or two halogen.' R7-1 is hydrogen, Ca-Gcycloalkyl, heterocycle, or Ci-salkyl optionally substituted with hydroxy, Ca-ccycloalkyl, alkoxy, heterocycle, heteroaryl, Cc-naryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-aalkyl or Cinalkyl; and P' is Ca-HarylCi-salkyl;
275

comprising condensing' a compound of the formula

wherein Rc is one or two halogen; Rr>° is Ci-aalkyl; and P1 is Ce-i-mi-ylCi-salkyl;
with a racemic compound of the formula

wherein R'*1 is hydrogen, Ca-ecycloalkyl, heterocycle, or Ci-salkyl optionally substituted with hydroxj', C3-Gcycloalkyl, alkoxy, heterocycle, heteroaryl, Conaryl, or amino, wherein said amino may be optionally substituted with -C(0)Ci-salkyl or Ci-salkyl;

to form a racemic compound of formula (I_26).
wherein Re is halogen; and P1 is Ce-HarylCi-salkyli
comprising condensing a compound of the formula
48. A process for the preparation of a racemic compound of formula (1-27)

wherein Re is one or two halogen; R50 is Ci-salkyl; and PJ is Cfii-iarylCiBalkyi;
with a racemic compound of the formula
276

to form a racemic compound of formula (1-27).
49. A method of treatment of an HIV infection in a human comprising administering to said human an antiviral effective amount of a compound according to any of claims 1 to 33.
50. A compound as claimed in any of claims 1 to 33 for use in medical therapy.
51. Use of a compound as claimed in any of claims 1 to 33 in the manufacture of a medicament for the treatment or prophylaxis of an HIV infection.
52. A compound of formula (P20a) described in Claim 36. formula (P20b) described in Claim 37, formula (1-2la) described in Claim 38, formula (P21b) described in Claim 39, formula (P22a) described in Claim 40, formula (I-22b) described in Claim 41, formula (P23a) described in Claim 42, formula Cf-23b) described in Claim 43, formula (P24a) described in Claim 44, formula (I-24b) described in Claim 45, formula (1-2.5) described in Claim 46, formula (P26) described in Claim 47, or formula (1-27) described in Claim 48, or a pharmaceutical acceptable salt thereof.
53. A compound of formula (I'20a) described in Claim 36. formula (I-20b) described in Claim 37, formula (I-21a) described in Claim 38, formula (I-21b) described in Claim 39, formula (I'22a) described in Claim 40, formula (P22b) described in Claim 41, formula (P23a) described in Claim 42, formula (P23b) described in Claim 43, formula (P24a) described in Claim 44, formula (P24b) described in Claim 45, formula (1-25) described in Claim 46, formula (1-26) described in Claim 47, or formula (1-27) described in Claim 48, or a pharmaceutical acceptable salt thereof, wherein each P1 is hydrogen.
54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors.
55. A method of treatment of an HIV infection in a human comprising administering to said human a composition comprising a compound according to any of claims 1 to
277

33 and another therapeutic agent.
56. The method according to claim 55 wherein said therapeutic agent is selected from reverse transcriptase inhibitors and protease inhibitors.
278

The present invention is to provide a novel compound (I) shown below, having the anti-virus activity, particularly the HIV integrase inhibitory activity, and a drug containing the same, particularly an anti-HIV drug, as well as a process and an intermediate thereof.

(wherein
Z1 is NR4;
R1 is hydrogen or lower alkyl;
X is a single bond, a hetero atom group selected from O, S, SO, SO2 and NH, or lower alkylene or lower alkenylene in which the hetero atom group may intervene;
R2 is optionally substituted aryl;
R3 is hydrogen, a halogen, hydroxy, optionally substituted lower alkyl etc; and
R4 and Z2 part taken together forms a ring, to form a polycyclic compound,

including e.g., a tricyclic or tetracyclic compound.

Back