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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/08, 401/14, A61K 31/47

A1

(11) International Publication Number: **WO 99/07706**

(43) International Publication Date: 18 February 1999 (18.02.99)

(21) International Application Number: PCT/KR98/00246

(22) International Filing Date: 8 August 1998 (08.08.98)

(30) Priority Data:
1997/38036 9 August 1997 (09.08.97) KR

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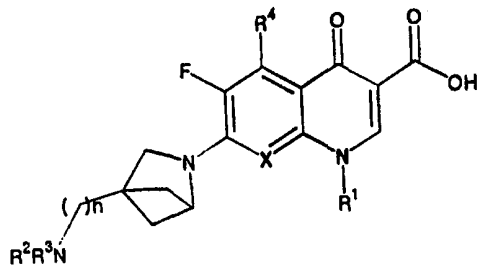
(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: QUINOLONE CARBOXYLIC ACID DERIVATIVES



(I)

(57) Abstract

A quinolone carboxylic acid derivative of formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{1-4}alkyl group optionally substituted with one or more halogens, a cyclopropyl group optionally substituted with a C_{1-4}alkyl group, or a phenyl group optionally substituted with one or more halogens; X is N or CY (wherein Y is H, halogen or C_{1-4}alkoxy), or forms $-COCH_2CH(CH_3)-$ group together with R^1; R^2 and R^3 are each independently H or a C_{1-4}alkyl group optionally substituted with one or more halogens; R^4 is H or an amino group; and n is 0 or 1.

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QUINOLONE CARBOXYLIC ACID DERIVATIVES

Field of the Invention

The present invention relates to novel quinolone carboxylic acid derivatives and pharmaceutically acceptable salts thereof having an excellent antibacterial activity, a process for preparing same, and an antibacterial composition containing same as an active ingredient.

Background of the Invention

Many quinolone derivatives are known to exhibit high antibacterial activities(see U.S. Patent No. 5,631,266; European Patent Publication Nos. 078,362 and 270,904; and German Patent Publication No. 3,906,365). However, some of the conventional quinolone compounds have limited activities against Gram-positive bacteria, while other quinolone derivatives exhibit the problem of poor water-solubility or side effects such as high cytotoxicity.

The present inventors have, therefore, endeavored to develop non-toxic compounds having a higher potency against a broad spectrum of bacteria; and have unexpectedly found that certain quinolone carboxylic acid derivatives having a 3-azabicyclo[2.1.1]hexane amine moiety at the 7-position of the quinolone nucleus exhibit a broad spectrum antibacterial activity and reduced cytotoxicity.

Summary of the Invention

It is, therefore, a primary object of the present invention to provide novel quinolone carboxylic acid derivatives, pharmaceutically acceptable salts thereof, having a potent antibacterial activity, especially against Gram-positive bacteria, with a low cytotoxicity.

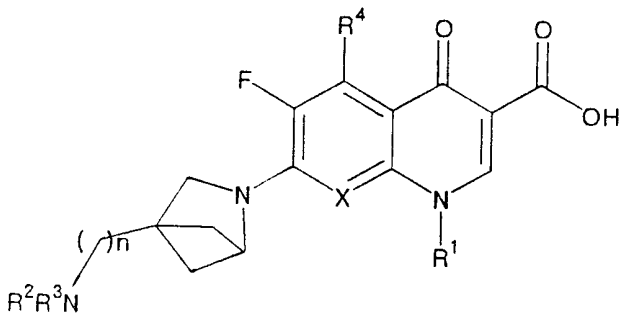
It is another object of the present invention to provide an antibacterial composition containing one or more

of the inventive compounds as an active ingredient.

It is a further object of the present invention to provide a process for the preparation of the inventive novel compounds.

It is still another object of the invention to provide novel intermediate compounds useful for the preparation of the inventive compounds.

In accordance with the present invention, there is provided a quinolone carboxylic acid derivative of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

R^1 is a C_{1-4} alkyl group optionally substituted with one or more halogens, a cyclopropyl group optionally substituted with a C_{1-4} alkyl group, or a phenyl group optionally substituted with one or more halogens;

X is N or CY(wherein Y is H, halogen or C_{1-4} alkoxy), or forms $-COCH_2CH(CH_3)-$ group together with R^1;

R^2 and R^3 are each independently H or a C_{1-4} alkyl group optionally substituted with one or more halogens;

R^4 is H or an amino group; and

n is 0 or 1.

Detailed Description of the Invention

Among the compounds of the present invention, preferred are those wherein: R^1 is an ethyl, fluorine-substituted ethyl, cyclopropyl or halogen-substituted phenyl group; and R^2 and R^3 are each independently H, CH_3 or

a fluorine-substituted ethyl group.

Particularly preferred compounds of the present invention are:

1-cyclopropyl-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo-[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

9-fluoro-2,3-dihydro-3-methyl-10-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-N-methylamino-methyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-(2,4-difluorophenyl)-6-fluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid;

1-(2-fluoroethyl)-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-amino-3-azabicyclo-[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-6-fluoro-8-methoxy-7-(1-N-(2-fluoroethyl)amino-methyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

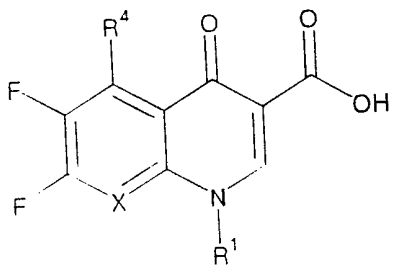
1-cyclopropyl-6-fluoro-8-chloro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid; and pharmaceutically acceptable salts thereof.

The present invention further includes, within its scope, pharmaceutically acceptable salts of the compounds of formula(I). The non-toxic salts which fall within the scope of the present invention include inorganic acid salts

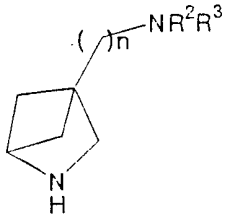
such as hydrochloride, sulfate, phosphate and nitrate, and organic acid salts such as tartrate, fumarate, citrate, mesylate and acetate.

The pharmaceutically acceptable salt of the present invention may be prepared in accordance with a known method, e.g., by reacting the compound of formula(I) with a suitable acid in the presence of a solvent, e.g., methanol, ethanol, dichloromethane, ethyl acetate or diethyl ether.

The compound of formula(I) may be prepared by a process which comprises reacting a compound of formula(II) with a compound of formula(III) in a suitable solvent in the presence of a base:



(II)



(III)

wherein, R^1, R^2, R^3, R^4, X and n have the same meanings as defined above.

The condensation reaction of compounds (II) and (III) may be conducted at a temperature ranging from 20 to 120°C.

Exemplary solvents which may be suitably used in the process of the present invention include acetonitrile, dimethylformamide, dimethylsulfoxide and pyridine.

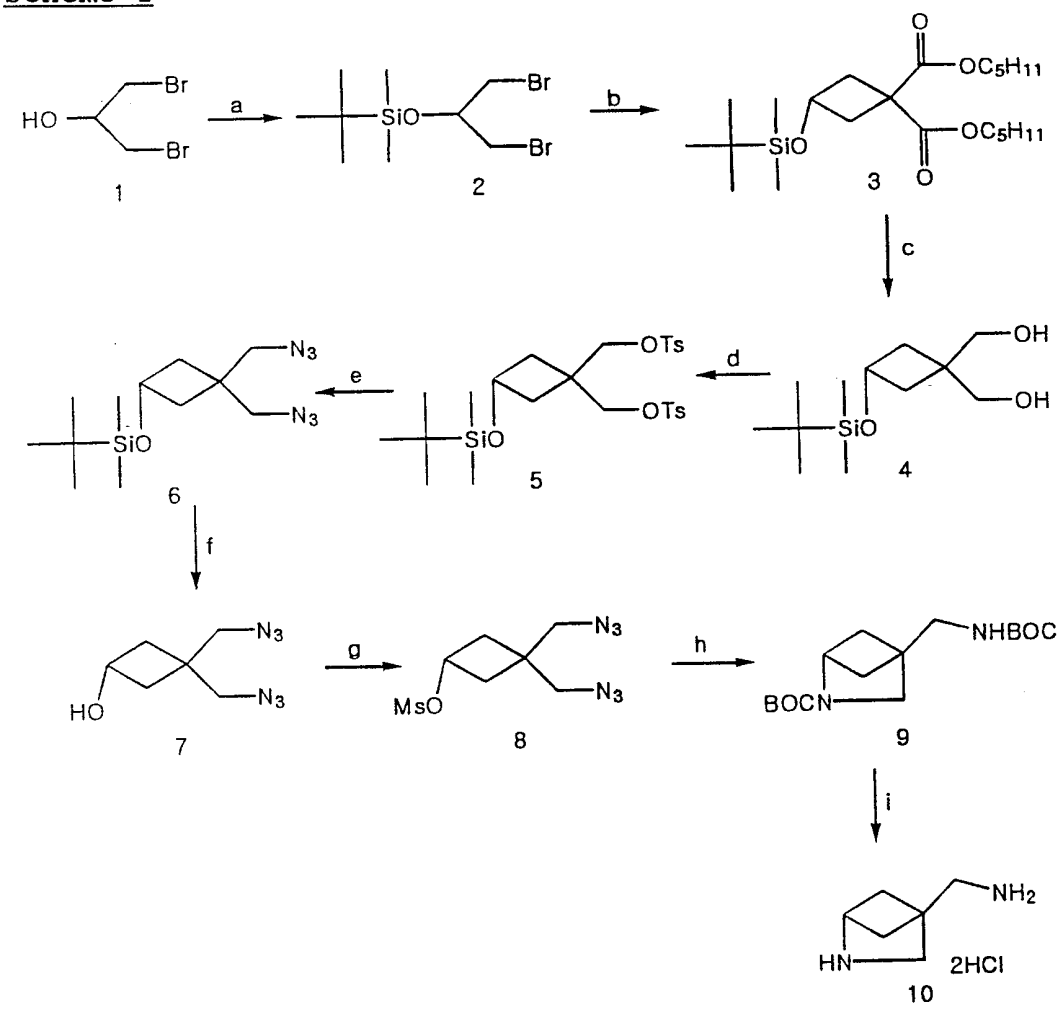
The base which can be used in practicing the present invention may be an inorganic base, or an organic base such as triethylamine, pyridine, diazabicyclo[5.4.0]undec-7-ene and diisopropylamine.

The compound of formula(II) may be prepared in accordance with a known method(see Chem. Pharm. Bull., 34, 4098(1986); J. Hetero., Chem., 24, 181; J. Med. Chem., 31, 503(1988); European Patent Publication No. 115,841; and Japanese Laid-open Patent Publication No. 62-252772).

The compound of formula(III) useful as an intermediate for the preparation of the compound of formula(I) is novel, and, therefore, it is encompassed within the scope of the present invention.

The novel compound of formula(III) of the present invention may be prepared in accordance with any one of the methods shown in Schemes 1 to 4.

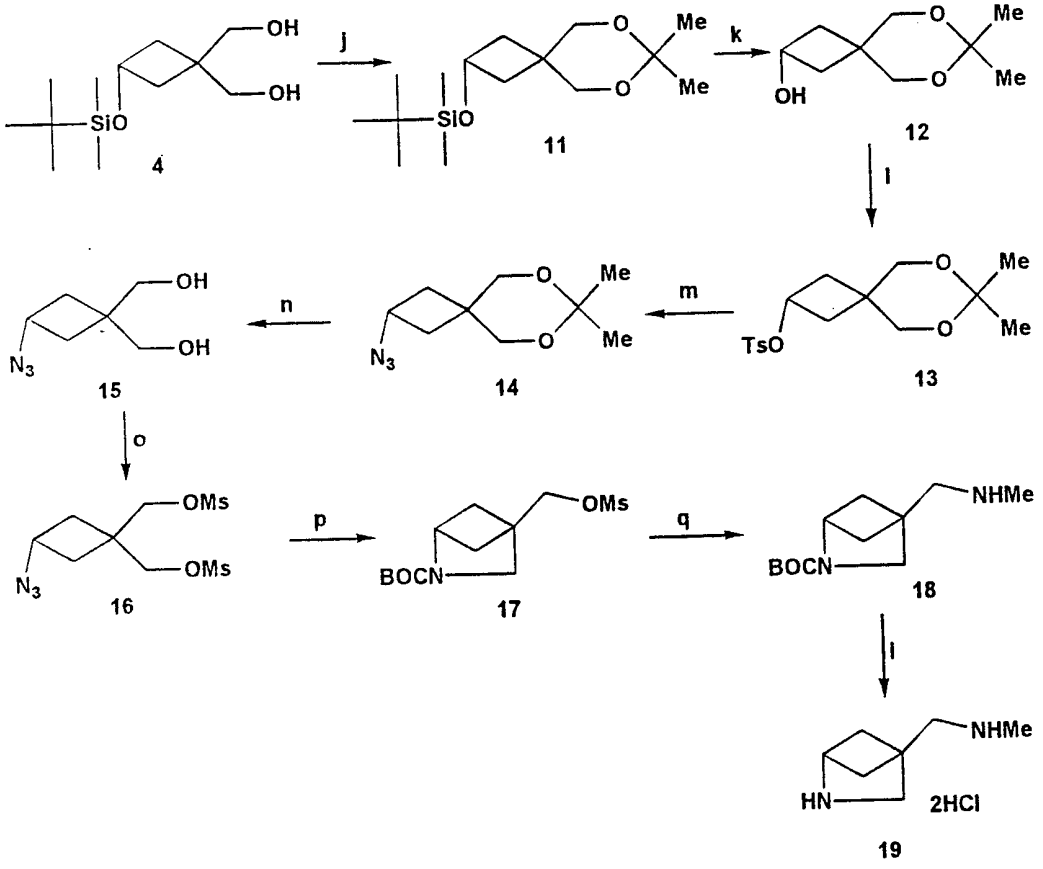
Scheme 1



wherein Ts is a toluenesulfonyl group, Ms is a methanesulfonyl group, and BOC is a t-butoxycarbonyl group.

In Step (a) of Scheme 1, dibromopropane (1) is silylated to give a compound of formula(2), which is converted to a compound of formula(3) in Step (b). In Step (c), the compound of formula(3) is reduced to give a compound of formula(4), followed by tosylation and azidation in Steps (d) and (e), respectively. Then, in Step (f), the compound of formula(6) is converted to a compound of formula(7), followed by methanesulfonylation to give a compound of formula(8) in Step (g). In Step (h), a compound of formula(9) having an azabicyclo[2.1.1]hexane ring is formed, which is then converted to 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl of formula(10) in Step i.

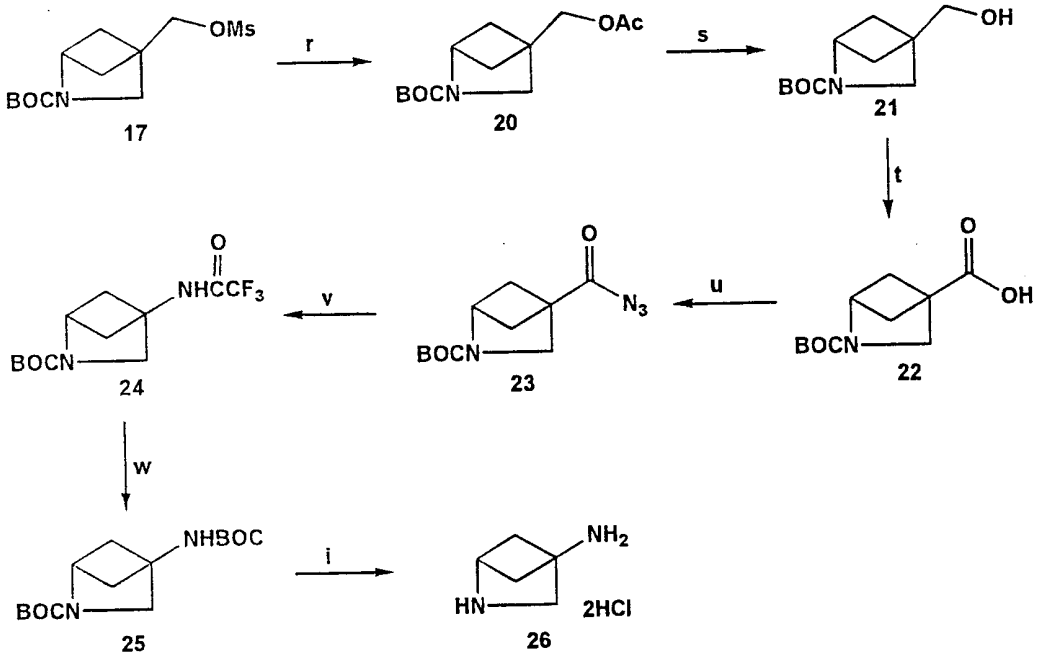
Scheme 2



wherein Me is a methyl group and Ms and BOC have the same meanings as defined above.

In Step (j) of Scheme 2, the compound of formula (4) prepared in Step (c) of Scheme 1, is refluxed with 2,2-dimethoxypropane in dimethylformamide in the presence of p-toluenesulfonic acid to give a spiro compound of formula(11) and the silyl group of the compound of formula(11) is removed to provide the compound of formula(12) in Step (k). In Steps (l) and (m), the compound of formula(12) is subjected to tosylation and azidation reactions, respectively. The compound of formula(14) is converted to a diol of formula(15) in Step (n), followed by methanesulfonylation of the diol to give the compound of formula(16). Subsequently, in Step (p), an azabicyclo[2.1.1]hexane derivative of formula(17) is formed, which is reacted with methylamine to give the compound of formula(18) in Step (q). Then, the protecting group of the compound of formula(18) is removed and acidified to give 1-N-methylaminomethyl-3-azabicyclo[2.1.1]-hexane·2HCl of formula(19) in Step i.

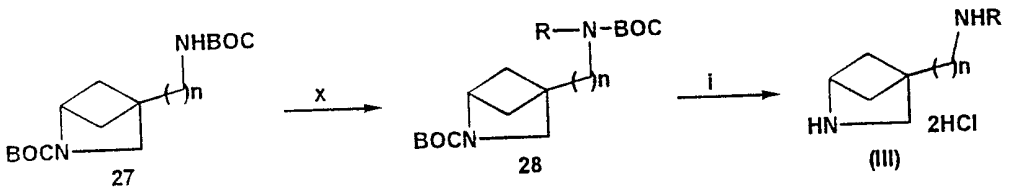
Scheme 3



wherein Ac is an acetate, and Me and BOC have the same meanings as defined above.

In Step (r) of Scheme 3, the mesylate group of the compound of formula (17) prepared in Step (p) of Scheme 2 is replaced with an acetate group to give the compound of formula(20), which is then converted to an alcohol of formula(21) in Step (s). In Step (t), the alcohol is oxidized to give an acid formula(22), which is subjected to azidation in Step (u). Then, in Step (v), the compound of formula(23) is converted to a compound of formula(24) and the compound of formula(24) is reacted with di-t-butyl dicarbonate to give the compound of formula(25) in Step (w). In Step (i), the protecting groups of the compound of formula(25) are removed and acidified to give 1-amino-3-azabicyclo[2.1.1]-hexane·2HCl of formula(26).

Scheme 4



wherein R is H or a C_{1-4} alkyl group optionally substituted with one or more halogens, and BOC and n have the same meanings as defined above.

In Step (x) of Scheme 4, the compound of formula (27) is alkylated to give the compound of formula (28), and then, in Step (i), the protecting groups of the compound of formula(28) are removed and acidified to give the compound of formula(III') wherein R and n have the same meanings as defined above.

The compounds of the present invention may be administered, either orally or intraperitoneally, in an effective amount ranging from 0.01 mg/kg to 100 mg/kg, preferably from 0.01 mg/kg to 50 mg/kg to a subject patient per day.

The present invention also includes within its scope an antibacterial composition comprising one or more of the inventive compounds as an active ingredient, in association with a pharmaceutically acceptable carrier, excipient and/or other additives, if necessary. The active ingredient present in the composition may range from 5 % to 50 % by weight thereof.

The following Examples are given for the purpose of illustration only, and are not intended to limit the scope of the invention.

Example 1: 1-Aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl

Step 1: 2-t-Butyldimethylsilyloxy-1,3-dibromopropane.

A mixture of 500ml of anhydrous methylene chloride, 50g of 1,3-dibromo-2-propanol(0.32ml), 43g of t-butyldimethylchlorosilane and 16g of imidazole was stirred at room temperature for 10 hours. 300 ml of water was added thereto, and the resulting mixture was extracted twice with 200ml portion of methylene chloride. The combined extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=5:1) to give 68g of the title compound as an oil.

^{1}H NMR($CDCl_3$) : δ 0.10(s, 6H), 0.58(s, 9H), 3.43(d, 4H), 4.04-3.92(m, 5H)

Step 2: Diisoamyl 3-t-butyldimethylsilyloxy-1,1-cyclobutanedicarboxylate

12g of sodium was digested in 500ml of isoamyl alcohol. To this solution, 90ml of diethyl malonate was added and ethanol produced was distilled off. 68g of 2-t-butyldimethylsilyloxy-1,3-dibromopropane was added dropwise to the mixture at 0°C, and refluxed for 18 hours. The excess isoamyl alcohol was removed under a reduced

pressure, water was added to the residue and the mixture was extracted twice with ethyl ether. The combined extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure. The residue was distilled at 175-179°C/0.4mmHg to give 68g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$) : δ 0.002(s, 6H), 0.84(s, 9H), 0.86-0.90(d, 12H), 1.43-1.47(m, 4H), 1.50-1.70(m, 2H), 2.37-2.48(m, 2H), 2.81(m, 2H), 4.09-4.17(m, 4H), 4.26-4.34(m, 1H).

Step 3: 1,1-Dihydroxymethyl-3-(t-butyldimethylsilyloxy)-cyclobutane

A 1 l round flask was charged with 9.84g of lithium aluminum and 500ml of ethyl ether under a nitrogen atmosphere, and 68g of diisoamyl 3-t-butyldimethylsilyloxy-1,1-cyclobutane dicarboxylate was added dropwise thereto at room temperature, followed by stirring the resulting mixture for 1 hour. A small amount of water was added thereto at 0°C, and the resulting mixture was extracted with ethyl ether. The ether extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=2:1), to give 30g of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ -0.01(s, 6H), 0.83(s, 9H), 1.66-1.75(m, 2H), 2.13-2.23(m, 2H), 3.65(s, 2H), 3.68(s, 2H), 4.18-4.32(m, 1H)

Step 4: 1,1-Di-p-toluenesulfonyloxymethyl-3-t-butyl-dimethylsilyloxycyclobutane

37g of p-toluenesulfonylchloride, 2.35g of dimethylaminopyridine and 27ml of triethylamine were mixed in 300ml of anhydrous methylene chloride. 19g of 1,1-dihydroxymethyl-3-t-butyldimethylsilyloxy-cyclobutane was added dropwise thereto and the mixture was reacted at room

temperature overnight. 300ml of water was added thereto, and the resultant was extracted twice with 200ml portion of ethyl ether. The combined ether extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1), to give 35g of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ -0.01(s, 6H), 0.80(s, 9H), 1.63-1.73(m, 2H), 2.07-2.18(m, 2H), 2.44(s, 6H), 3.90(s, 2H), 3.92(s, 2H), 4.05-4.16(s, 1H), 7.25-7.77(m, 8H)

Step 5: 1,1-Diazidomethyl-3-t-butyldimethylsilyloxy-cyclobutane

20 of sodium azide was suspended in 200ml of dimethyl-formamide and 35g of 1,1-di-p-toluenesulfonyloxymethyl-3-t-butyldimethylsilyloxycyclobutane was added thereto, and the mixture was stirred at 100°C for 2 hours. The reaction mixture was cooled to room temperature and poured into 300ml of water, and then, the mixture was extracted three times with 200ml portion of diethyl ether. The combined extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=7:1), to give 18g of the title compound.

^{1}H NMR($CDCl_3$) : δ 0.006(s, 6H), 0.84(s, 9H), 1.72-1.83(m, 2H), 2.13-2.24(m, 2H), 3.36(s, 2H), 3.39(s, 2H), 4.21-4.31(m, 2H)

Step 6: 1,1-Diazidomethyl-3-hydroxycyclobutane

18g of 1,1-diazidomethyl-3-t-butyldimethyl-silyloxycyclobutane and 77ml of tetrabutylammonium chloride was mixed in 200 ml of tetrahydrofuran(THF) and the mixture was stirred at room temperature for 30 minutes. After

removing THF under a reduced pressure , the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1), to give 10g of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.75-1.85(m, 2H), 2.18-2.24(m, 2H), 2.26(br, 1H). 3.36(s, 2H), 3.39(s, 2H), 4.21-4.31(m, 1H), 7.25-7.77(m, 8H)

Step 7: 1,1-Diazidomethyl-3-methanesulfonyloxycyclobutane

100g of 1,1-diazidomethyl-3-hydroxycyclobutane and 10ml of triethylamine were dissolved in 200ml of anhydrous methylene chloride, 5.64ml of methanesulfonyl chloride was added dropwise at -10°C and the mixture was stirred at 0°C for 40 minutes. 200 ml of water was added thereto and the mixture was extracted twice with 100ml portion of methylene chloride. The combined extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=1:1), to give 14g of the title compound.

^{1}H NMR($CDCl_3$) : δ 2.14-2.25(m, 2H), 2.34-2.44(m, 2H), 2.96(s, 3H). 3.40(s, 2H), 3.41(s, 2H), 4.91-5.05(m, 1H)

Step 8: 3-N-(t-butoxycarbonyl)-1-(N-t-butoxycarbonyl-aminomethyl)-3-azabicyclo[2.1.1]hexane

14g of 1,1-diazidomethyl-3-methanesulfonyloxy-cyclobutane was dissolved in 400ml of anhydrous methanol and 2.8g of 10% Pd-C was added thereto. The mixture was stirred for 20 hours under H_2 at 60 Psi and Pd-C was filtered off through cellite. To the filtrate, 27 g of di-t-butyl dicarbonate and 10ml of triethylamine were added, which was stirred at room temperature for 5 hours. After removing the solvent under a reduced pressure, the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1), to give 10.4g of the title

compound as a white crystal.

^{1}H NMR($CDCl_3$) : δ 1.41(m, 20H) 1.67-1.69(m, 2H), 3.15(s, 2H), 3.33-3.34(d, 2H), 4.24-4.30(m, 1H), 4.68(m, 1H).

Step 9: 1-Aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl

1g of 3-N-(t-butoxycarbonyl)-1-(N-t-butoxycarbonyl-aminomethyl)-3-azabicyclo[2.1.1]hexane was added to 10ml of 16% HCl/methanol solution, and the mixture was stirred at room temperature overnight. The resulting precipitate was filtered at a reduced pressure, washed with methanol and dried to give 0.37g of the title compound as a white solid.

^{1}H NMR(D_2O) : δ 1.57-1.63(m, 2H) 2.10(m, 2H), 3.30(s, 2H), 3.32(s, 2H), 4.18-4.19(m, 1H)

Example 2: 1-N-methylaminomethyl-3-azabicyclo[2.1.1]-hexane·2HCl

Step 1: 2-(t-Butyldimethylsilyloxy)-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane

26g of 1,1-dihydroxymethyl-3-(t-butyldimethylsilyl-oxy)-cyclobutane was dissolved in 1 l of THF and 2.4g of p-TsOH·H_2O(p-toluenesulfonic acid monohydrate) and 13.46g of 2,2-dimethoxypropane were added thereto, and the mixture was stirred at room temperature for 150 minutes. The solvent was removed under a reduced pressure, water was added to the residue, and the mixture was extracted with ether. The extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=3:1) to give 25g of the pure title compound as a colorless oil.

^{1}H NMR($CDCl_3$) : δ 0.003(s, 6H), 0.848(s, 9H), 1.362(s, 6H), 1.65-1.74(m, 2H), 2.17-2.27(m, 2H), 3.36(s, 2H), 3.68(s,

2H), 4.14-4.25(m, 1H)

Step 2: 2-Hydroxy-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane

A mixture of 25g of 2-(t-butyldimethylsilyloxy)-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane and 165ml of tetrabutylammonium chloride in 200ml of THF was stirred at room temperature for 40 minutes. The solvent was removed and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=2:1), to give 13g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$) : δ 1.34(s, 6H), 1.61-1.71(m, 2H), 2.20-2.30(m, 2H), 2.54(br, 1H), 3.65(s, 2H), 3.66(s, 2H), 4.20-4.30(m, 1H)

Step 3: 2-p-Toluenesulfonyloxy-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane

23g of 2-hydroxy-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane was dissolved in 500ml of methylene chloride and added thereto were 45g of p-toluenesulfonyl chloride, 2.47g of dimethylaminopyridine and 37ml of triphenylmethylamine. The reaction mixture was stirred at room temperature for 4 hours and water was added thereto. The resultant was extracted with methylene chloride, dried over anhydrous magnesium sulfate and distilled under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1) to give 39g of the title compound as a white crystal.

^{1}H NMR($CDCl_3$) : δ 1.32(s, 6H), 1.85-1.95(m, 2H), 2.16-2.27(m, 2H), 2.42(s, 3H), 3.61(s, 2H), 3.63(s, 2H), 4.70-4.84(m, 1H), 7.28-732(d, J=8.4, 2H), 7.72-7.76(d, J=8.4, 2H)

Step 4: 2-Azido-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane

39g of 2-p-toluenesulfonyloxy-7,7-dimethyl-6,8-dioxaspiro-[3.5]nonane was dissolved in 500ml of dimethylformamide and 37g of sodium azide was added thereto, and the mixture was stirred at 100°C for 1 hour. Water was added thereto, and the resultant was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=5:1), to give 23g of the title compound as a colorless oil.

^{1}H NMR($CDCl_3$) : δ 1.34(s, 6H), 1.77-1.88(m, 2H), 2.18-2.29(m, 2H), 3.66(s, 2H), 3.68(s, 2H), 3.77-3.92(m, 1H)

Step 5: 1-Azido-3,3-dihydroxymethylcyclobutane

16 g of 2-azido-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane was dissolved in 250ml of methanol, 4.8g of p-TsOH·H_2O were added thereto, and the mixture was stirred at room temperature for 4 hours. The solvent was removed, 200ml of water was added to the residue, and the mixture was extracted with ether. The extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=1:1) to give 12g of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ 1.86-1.97(m, 2H), 2.22-2.30(m, 2H), 3.71(s, 4H), 3.84-3.96(m, 1H)

Step 6: 1-Azido-3,3-(dimethanesulfonyloxymethyl)cyclobutane

24ml of triphenylmethylamine was added to a solution of 1.1g of 1-azido-3,3-dihydroxymethylcyclobutane dissolved in 20ml of anhydrous methylene chloride, and then, methanesulfonyl chloride was added dropwise thereto at

-10°C. The reaction mixture was stirred at 0°C for 1 hour, water was added thereto, and extracted with methylene chloride. The extract was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=1:1) to give 1.97g of the title compound as a yellow oil.

^{1}H NMR($CDCl_3$) : δ 2.07-2.09(m, 2H), 2.30-2.27(m, 2H), 3.00(s, 6H). 3.93-4.03(s, 2H), 4.16(s, 2H), 4.17(s, 2H)

Step 7: 1-Methanesulfonyloxymethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

0.2g of Pd-C was added to a solution of 1.97g of 1-azido-3,3-(dimethanesulfonyloxymethyl)cyclobutane dissolved in 200ml of methanol, and the mixture was stirred overnight under H_2 at 60 psi. Pd-C was filtered off through cellite and the solvent was removed from the filtrate. The residue was dissolved in a small amount of methanol and 120ml of toluene was added thereto, and the mixture was refluxed for 20 hours. The reaction mixture was cooled to room temperature and 1.67g of di-t-butyl dicarbonate and 1ml of triethylamine were added thereto. The mixture was stirred at room temperature for 1 hour and the solvent was removed. Water and ethyl acetate were added to the residue and the organic extract was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1), to give 0.66g of the title compound as a white crystal.

^{1}H NMR($CDCl_3$) : δ 1.45(s, 9H), 1.52-1.54(m, 2H), 1.86-1.87(m, 2H), 3.01(s, 3H), 3.27(s, 2H), 4.38(s, 2H), 4.38(m, 1H).

Step 8: 1-(N-methyl)aminomethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

5ml of a 40% methylamine aqueous solution and 5 ml of methanol were added to 660mg of 1-methanesulfonyloxymethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane and the mixture was stirred overnight at room temperature. The solvent was removed, water and ethyl acetate were added to the residue and the organic extract was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (eluent: CH_2Cl_2:MeOH=6:1), to give 250mg of the title compound.

^1H NMR($CDCl_3$) : δ 1.19(m, 11H), 1.50(m, 2H), 2.20(s, 3H), 2.57(s, 2H), 2.96(s, 2H), 4.05(br, 1H).

Step 9: 1-(N-methyl)aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl

250mg of 1-(N-methyl)aminomethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was added to 10ml of 16% HCl/methanol and the mixture was stirred at room temperature for 10 hours. The solvent was removed under a reduced pressure to give 198mg of the title compound.

^1H NMR(D_2O) : δ 1.31(m, 2H), 2.00(m, 2H) 2.41(s, 3H), 2.80(s, 2H), 3.25(s, 2H), 4.05(br, 1H)

Example 3: 1-Amino-3-azabicyclo[2.1.1]hexane·2HCl

Step 1: 1-Acetoxymethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

4.8g of 1-(methanesulfonyloxy)methyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane of Step 7 of Example 2 was dissolved in dimethylformamide. 4.85g of potassium acetate was added thereto and the resulting mixture was stirred at 70°C for 1 hour, before extracting

with water and ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=1:1) to give 4.4g of the pure title compound as a yellow oil.

^{1}H NMR($CDCl_3$) : δ 1.39(s, 9H), 1.45(m, 2H), 1.74(m, 2H), 2.00(s, 3H), 3.17(s, 2H), 4.19(m, 1H)

Step 2: 1-Hydroxymethyl-3-N-t-butoxycarbonyl-3-aza-bicyclo[2.1.1]hexane

4.4g of 1-acetoxymethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was dissolved in 20ml of ethanol, and stirred at 0°C. 3g of potassium hydroxide was dissolved in a small amount of water, diluted with ethanol and added to the mixture, followed by neutralization with 10% sulfuric acid. Ethanol was removed and the residue was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=1:1), to give 3.7g of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ 1.40(m, 2H), 1.42(s, 9H), 1.76(m, 2H), 2.45(s, 1H, OH), 3.20(s, 2H), 3.76(s, 2H), 4.30(m, 1H)

Step 3: 3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexyl-1-carboxylic acid

3.4g of 1-hydroxymethyl-3-N-t-butoxylcarbonyl-3-azabicyclo[2.1.1]hexane and 21.6g of pyridinium dichromate were added to 45ml of dimethylformamide. The mixture was stirred at room temperature for 5 hours and filtered. Water and ethylacetate were added to the filtrate and shaken. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated under a

reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=6:1) to give 2.24g of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ 1.44(s, 9H), 1.73(m, 2H), 2.18(m, 2H), 3.50(s, 2H), 4.32(m, 1H)

Step 4: 1-Azidocarbonyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

1g of 3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexyl-1-carboxylic acid was dissolved in 15ml of dichloromethane. 1.14g of diphenylphosphoroazide and 0.68ml of triethylamine were added thereto. The mixture was stirred at room temperature for 3 hours and water was added thereto. The resultant was extracted twice with dichloromethane, the combined extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1), to give 647mg of the title compound.

^{1}H NMR(CD_3OD) : δ 1.46(s, 9H), 1.69(m, 1H), 1.73(m, 1H), 2.10-2.23(m, 2H), 3.30(m, 1H), 3.45(m, 1H), 4.20-4.37(m, 1H).

Step 5: 1-(N-trifluoromethylcarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

647mg of 1-azidocarbonyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was dissolved in 10ml of dichloromethane and 0.24ml of trifluoroacetate was added thereto. The mixture was refluxed for 24 hours and cooled. The solvent was removed and 3ml of triethylamine in methanol and 2.0g of di-t-butyl dicarbonate were added thereto. The mixture was stirred at room temperature for 5 hours, methanol was removed, and then, water and ethyl acetate were added to the residue. The organic extract was

dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=3:1) to give 281mg of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ 1.40(s, 9H), 1.88(m, 2H), 2.10(m, 2H), 3.43(s, 2H), 4.30(m, 1H), 6.73(s, 1H, NH)

Step 6: 1-(N-t-butoxycarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

407mg of 1-(N-trifluoromethylcarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was dissolved in a mixture of water and methanol(2:8) and 320mg of potassium carbonate was added thereto, and the mixture was stirred at room temperature overnight. After the starting material was all consumed, 450mg of di-t-butyl dicarbonate (2.07mmol) was added to the reaction mixture, and stirred at room temperature for 8 hours. After removing methanol, water and ethyl acetate were added to the mixture and was shaken. The organic extract was dried over anhydrous magnesium sulfate and concentrated under a reduced pressure and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=2:1) to give 388mg of the title compound as a white solid.

^{1}H NMR($CDCl_3$) : δ 1.42(s, 9H), 1.43(s, 9H), 1.75(m, 2H), 2.02(m, 2H), 3.32(s, 2H). 4.25(m, 1H), 5.00(br, 1H, NH)

Step 7: 1-amino-3-azabicyclo[2.1.1]hexane·2HCl

368mg of 1-(N-t-butoxycarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was added to 5ml of 37% HCl/methanol and the mixture was stirred overnight. The resulting precipitate were filtered to give 188mg of the title compound as a white solid.

^{1}H NMR(D_2O) : δ 1.86(m, 1H), 1.88(m, 1H), 2.26(m, 2H),

3.37(s, 2H), 4.20(m, 1H).

Example 4: 1-(N-methyl)amino-3-azabicyclo[2.1.1]hexane·2HCl

Step 1: 1-(N-methyl-N-t-butoxycarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

3g of 1-(N-t-butoxycarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane obtained in Step 6 of Example 3 was dissolved in 30ml of dimethylformamide and 0.7g of 60% sodium hydride was added thereto, and the mixture was stirred for 3 hours. 1.1g of methyl iodide was added to the mixture and the resultant was stirred at room temperature for 5 hours. The reaction mixture was added to 100 ml of water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and the residue was purified by silica gel column chromatography(eluent: hexane:ethyl acetate=5:1) to give 3.5g of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.42(s, 9H), 1.43(s, 9H), 1.75(m, 2H), 2.02(m, 2H), 2.70(s, 3H), 3.32(s, 2H). 4.25(m, 1H)

Step 2: 1-(N-methyl)amino-3-azabicyclo[2.1.1]hexane·2HCl

1.5g of 1-(N-methyl-N-t-butoxycarbonyl)amino-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was added to 5ml of 37% HCl/methanol and the mixture was stirred overnight. The resulting precipitate were filtered to give 1.8g of the title compound as a white solid.

^{1}H NMR(D_2O) : δ 1.86(m, 1H), 1.88(m, 1H), 2.26(m, 2H), 2.36(s, 3H), 3.37(s, 2H)

Example 5: 1-(N-2-fluoroethyl)aminomethyl-3-azabicyclo-[2.1.1]hexane·2HCl

Step 1: 1-(N-2-fluoroethyl-N-t-butoxycarbonyl)aminomethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane

1.6g of 1-(N-t-butoxycarbonyl)aminomethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane obtained in Step 8 of Example 1 was dissolved in 15ml of dimethylformamide and 0.4g of 60% sodium hydride was added thereto, and the mixture was stirred for 3 hours. Then, 0.9g of 1-fluoro-2-chloroethane was added to the mixture and the resultant was stirred at room temperature for 14 hours. The reaction mixture was added to 60 ml of water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=5:1) to give 1.78g of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.42(s, 9H), 1.43(s, 9H), 1.75(m, 2H), 2.02(m, 2H), 2.70(s, 3H), 3.32(s, 2H)

Step 2: 1-(N-2-fluoroethyl)aminomethyl-3-azabicyclo[2.1.1]-hexane·2HCl

1.0g of 1-(N-2-fluoroethyl-N-t-butoxycarbonyl)-aminomethyl-3-N-t-butoxycarbonyl-3-azabicyclo[2.1.1]hexane was added to 5ml of 37% HCl/methanol and the mixture was stirred overnight. The resulting precipitates were filtered to give 0.6g of the title compound as a white solid.

^{1}H NMR(D_2O) : δ 1.86(m, 1H), 1.88(m, 1H), 2.26(m, 2H), 2.36(s, 3H), 3.37(s, 2H)

Example 6: 1-Cyclopropyl-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo-[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

280mg of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-

oxoquinoline-3-carboxylic acid and 220mg of 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, 417mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto, and the mixture was refluxed for 6 hours. The resulting crystal was filtered, washed with acetonitrile and dried to give 280mg of the title compound as a light yellow crystal.

^{1}H NMR(CF_3COOD) : δ 1.55-1.59(m, 2H), 1.71-1.76(m, 2H), 2.06-2.15(m, 2H), 2.46-2.53(m, 2H), 3.94(s, 2H), 4.25(s, 2H), 4.63-4.68(m, 1H), 5.43(m, 1H), 8.24-8.26(d, 1H), 9.41(s, 1H).

Example 7: 1-Cyclopropyl-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid·2HCl

200mg of 1-cyclopropyl-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was added to 10ml of 16% HCl/methanol and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under a reduced pressure and ethyl ether was added thereto. The resulting crystalline material was filtered, washed thoroughly with ethyl ether and dried under a reduced pressure to give 160mg of the title compound as a yellow crystal.

^{1}H NMR(D_2O) : δ 1.04-1.23(m, 4H), 1.26-1.69(m, 2H), 1.96-2.05(m, 2H), 3.32(s, 2H), 3.59(s, 2H), 3.93-4.01(m, 1H), 4.54(m, 1H), 7.23-7.42(m, 1H), 8.52-8.61(m, 1H).

Example 8: 1-Cyclopropyl-5-amino-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 79mg of 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to

2ml of acetonitrile and 166mg of 1,8-diazabicyclo-[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to give 110mg of the title compound.

^{1}H NMR(CF_3COOD) : δ 1.38-1.41(m, 2H), 1.53-1.61(m, 2H), 2.01-2.10(m, 2H), 2.38-2.42(m, 2H), 3.82(s, 2H), 4.10(m, 2H), 4.40(m, 2H), 5.20(m, 1H), 9.20(s, 1H).

Example 9: 1-Cyclopropyl-5-amino-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid·2HCl

The procedure of Example 6 was repeated except that 110mg of 1-cyclopropyl-5-amino-6,8-difluoro-7-1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was used as a starting material to give 80mg of the title compound as a yellow solid.

^{1}H NMR(D_2O) : δ 0.81-0.89(m, 2H), 0.93-1.00(m, 2H), 1.49-1.51(m, 2H), 1.86-1.88(m, 2H), 3.18(s, 2H), 3.34(s, 2H), 3.69(m, 1H), 4.39-4.33(m, 1H), 5.32(m, 1H).

Example 10: 9-Fluoro-2,3-dihydro-3-methyl-10-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid

100mg of 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid and 79mg of 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 2ml of acetonitrile and 166mg of 1,8-diazabicyclo-[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to give 78mg of the title compound.

^{1}H NMR(CF_3COOD) : δ 1.82-1.84(m, 5H), 2.10-2.25(m, 2H), 3.57-3.36(m, 2H), 3.74-3.82(m, 2H), 4.47-4.58(m, 2H),

4.93(m, 1H), 5.28-5.35(m, 1H), 8.13-8.17(d, 1H), 9.45(s, 1H).

Example 11: 9-Fluoro-2,3-dihydro-3-methyl-10-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid·HCl

The procedure of Example 7 was repeated except that 70mg of 9-fluoro-2,3-dihydro-3-methyl-10-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid was used as a starting material to give 50mg of the title compound as a yellow solid.

^{1}H NMR(D_2O) : δ 1.37-1.40(m, 2H), 1.50(m, 2H), 1.87(m, 2H), 3.18(s, 2H), 3.37(m, 2H), 4.21(m, 1H), 4.76-4.81(m, 1H), 7.39(d, 1H), 8.65(s, 1H).

Example 12: 1-Cyclopropyl-5-amino-6,8-difluoro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

160mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 128mg of 1-N-methylaminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 2ml of acetonitrile and 206mg of 1,8-diazabicyclo-[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 was to give 136mg of the title compound.

^{1}H NMR(CF_3COOD) : δ 1.29-1.34(m, 2H), 1.43-1.47(m, 2H), 1.91(m, 2H), 2.29(m, 2H), 3.05(s, 3H), 3.68(s, 2H), 3.97(s, 2H), 4.30(m, 1H), 5.01(m, 1H), 9.10(s, 1H).

Example 13: 1-Cyclopropyl-5-amino-6,8-difluoro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid·HCl

The procedure of Example 7 was repeated except that 136mg of 1-cyclopropyl-5-amino-6,8-difluoro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was used as a starting material to obtain 100mg of the title compound as a yellow solid.

^{1}H NMR(D_2O) : δ 0.79-0.82(m, 2H), 1.01-1.12(m, 2H), 1.36(m, 2H), 1.69(m, 2H), 2.72(s, 3H), 3.13(s, 2H), 3.25(s, 2H), 3.70(m, 1H), 4.48(m, 1H), 8.68(s, 1H)

Example 14: 1-(2,4-Difluorophenyl)-6-fluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

120mg of 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 79mg of 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, and 166mg of 1,8-diazabicyclo-[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to obtain 110mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 2.06-2.15(m, 2H), 2.46-2.53(m, 4H), 3.94(s, 2H), 4.25(m, 1H), 7.26(m, 2H), 7.62(m, 1H), 8.28(d, 1H), 9.2(d, 1H), 11.6(s, 1H)

Example 15: 1-Cyclopropyl-6-fluoro-7-[(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

95mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 79mg of 1-N-methylaminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, and 166mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to obtain 101mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.35(m, 2H), 1.56(m, 2H), 2.07-2.18(m, 2H), 2.46-2.53(m, 7H), 3.94(s, 2H), 4.18(m, 1H), 4.21(m, 1H), 8.20(d, 1H), 8.20(d, 1H), 9.19(s, 1H), 11.5(s, 1H)

Example 16: 1-(2-Fluoroethyl)-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-(2-fluoroethyl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 79mg of 1-aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 3ml of acetonitrile, and 130mg of 1,8-diazabicyclo-[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to obtain 92mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 2.03-2.11(m, 2H), 2.40-2.51(m, 4H), 3.94(s, 2H), 4.22(m, 2H), 4.61(m, 2H), 5.20(m, 1H), 8.05(d, 1H), 9.38(s, 1H), 11.51(s, 1H)

Example 17: 1-Cyclopropyl-5-amino-6,8-difluoro-7-{(1-amino-3-azabicyclo[2.1.1]hexane)-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 79mg of 1-amino-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, and 126mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to obtain 113mg of the title compound.

^{1}H NMR(CF_3COOD) : δ 1.38(m, 2H), 1.54-1.60(m, 2H), 2.06(m, 2H), 2.38(m, 2H), 4.10(m, 2H), 4.40(m, 1H), 5.21(m, 1H), 9.21(s, 1H), 11.61(s, 1H)

Example 18: 1-Cyclopropyl-6-fluoro-8-methoxy-7-{1-N-(2-fluoroethyl)amino-methyl-3-azabicyclo[2.1.1]hex-3-yl}-1,4-

dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 120mg of 1-(N-2-fluoroethyl)aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, and 160mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the same procedure of Example 6 to obtain 123mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.19(m, 1H), 1.30(m, 1H), 1.48(m, 1H), 1.56(m, 1H), 2.06-2.14(m, 2H), 2.43-2.61(m, 4H), 3.36(m, 2H), 3.74(s, 3H), 3.94(s, 2H), 4.10(m, 1H), 4.56(m, 2H), 5.01(m, 1H), 8.05(d, 1H), 9.32(s, 1H), 11.52(s, 1H)

Example 19: 1-Cyclopropyl-6-fluoro-8-chloro-7-{(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hexane)-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 79mg of 1-N-methylamino-3-azabicyclo[2.1.1]hexane·2HCl were added to 5ml of acetonitrile, and 152mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the same procedure of Example 6 to obtain 103mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.40-1.60(m, 4H), 2.03-2.10(m, 2H), 2.40-2.61(m, 5H), 3.91(m, 2H), 4.21(m, 1H), 5.10(m, 1H), 8.14(d, 1H), 8.21(d, 1H), 9.01(s, 1H), 11.42(s, 1H)

Example 20: 1-Cyclopropyl-6-fluoro-8-chloro-7-{1-(N-methyl)aminomethyl-3-azabicyclo[2.1.1]hexane)-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

100mg of 1-cyclopropyl-6,7-difluoro-8-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 129mg of 1-(N-methyl)aminomethyl-3-azabicyclo[2.1.1]hexane·2HCl were

added to 5ml of acetonitrile, and 170mg of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. Then, the resultant was treated by the procedure of Example 6 to obtain 133mg of the title compound.

^{1}H NMR($CDCl_3$) : δ 1.60(m, 2H), 1.81(m, 2H), 2.07-2.2(m, 2H), 2.41-2.51(m, 5H), 3.94(m, 2H), 4.24(m, 2H), 4.28(m, 1H), 5.31(m, 1H), 8.28(d, 1H), 9.45(s, 1H), 11.57(s, 1H)

Test 1. Antibacterial activity in vitro

In order to measure antibacterial activities of the compounds of the present invention, minimal inhibitory concentrations(MIC, μg/ml) of representative compounds against standard strains were determined and compared with those of ciprofloxacin and sparfloxacin, which were used as control compounds.

The MIC values were determined employing a two-fold dilution method and Muller Hinton agar medium. Each of the Hoechst 345 standard strains having the concentration of 10^7CFU/ml was inoculated onto the medium, and incubated at 37°C for 18 hours.

The standard test strains used are as follows:

Gram-positive bacteria

1. Streptococcus pyogenes A 308
2. Streptococcus pyogenes A 77
3. Streptococcus faecium MD 8b
4. Staphylococcus aureus SG 511
5. Staphylococcus aureus 285
6. Staphylococcus aureus 503

The results of the MIC tests are shown in Table I.

Table I. Minimal Inhibitory Concentration(MIC) μg/ml

	Compound of Example		Cipro-floxacin	Spar-floxacin
	16	17		
Streptococcus pyogenes A 308	0.049	0.049	3.125	0.391
Streptococcus pyogenes A 77	0.025	0.025	0.781	0.195
Streptococcus faecium MD 8b	0.025	0.049	0.391	0.391
Staphylococcus aureus SG 511	0.007	0.007	0.195	0.098
Staphylococcus aureus 285	0.013	0.013	0.781	0.049
Staphylococcus aureus 503	0.007	0.013	0.391	0.049

note:

ciprofloxacin: 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid

sparfloxacin : 1-cyclopropyl-5-amino-6,8-difluoro-7-(3,5-dimethylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid

Test 2. Selectivity Index

Selectivity indexes of the compounds of the present invention and control compounds were measured using gyrase purified from of E. coli and calf thymus topoisomerase II obtained from Topogen. Co.

The selectivity index(S.I.) was calculated by the equation 1.

$$S.I. = \frac{IC_{100,\ Topo\ II}}{IC_{100,\ Gyrase}} \qquad \text{(Eq. 1)}$$

wherein, $IC_{100,\ Topo\ II}$ is the concentration of a compound to inhibit the enzyme activity of topoisomerase II and $IC_{100,\ Gyrase}$ is the concentration of a compound to inhibit the enzyme activity of gyrase of E. coli.

The results are shown in Table II.

Table II Selectivity Index

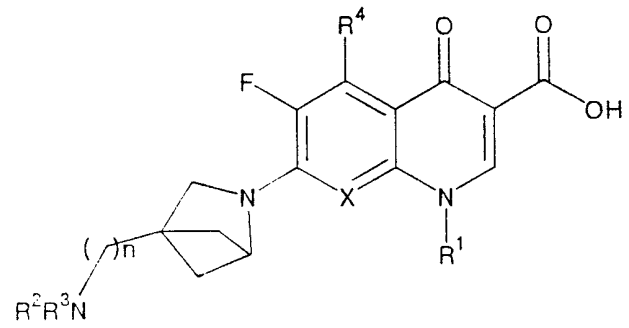
	$IC_{100,\ Topo\ II}$ ($\mu g/ml$)	$IC_{100,\ Gyrase}$ ($\mu g/ml$)	S.I.
Example 16	1,000	0.5	2,000
Example 17	1,000	0.4	2,500
Ciprofloxacin	500	0.5	1,000
Sparfloxacin	500	1.0	500

As can be seen from the Table I and II, the quinolone carboxylic acid derivatives of the present invention generally exhibit superior antibacterial activities against both Gram-positive and Gram-negative bacteria and much lower toxicities as compared with the control compounds.

While the embodiments of the subject invention have been described and illustrated, it is obvious that various changes and modifications can be made therein without departing from the spirit of the present invention which should be limited only by the scope of the appended claims.

What is claimed is:

1. A quinolone carboxylic acid derivative of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

R^1 is a C_{1-4} alkyl group optionally substituted with one or more halogens, a cyclopropyl group optionally substituted with a C_{1-4} alkyl group, or a phenyl group optionally substituted with one or more halogens;

X is N or CY(wherein Y is H, halogen or C_{1-4} alkoxy), or forms $-COCH_2CH(CH_3)-$ group together with R^1;

R^2 and R^3 are each independently H or a C_{1-4} alkyl group optionally substituted with one or more halogens;

R^4 is H or an amino group; and

n is 0 or 1.

2. The quinolone carboxylic acid derivative of claim 1, wherein: R^1 is an ethyl, fluorine-substituted ethyl, cyclopropyl or a halogen-substituted phenyl group; and R^2 and R^3 are each independently H, CH_3 or a fluorine-substituted ethyl group.

3. The quinolone carboxylic acid derivative of claim 1 selected from the group consisting of:

1-cyclopropyl-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo-[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

9-fluoro-2,3-dihydro-3-methyl-10-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-7-oxo-7H-pyrido[1,2,3-d,e]-1,4-benzoxazine-6-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-N-methylamino-methyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-(2,4-difluorophenyl)-6-fluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid;

1-cyclopropyl-6-fluoro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid;

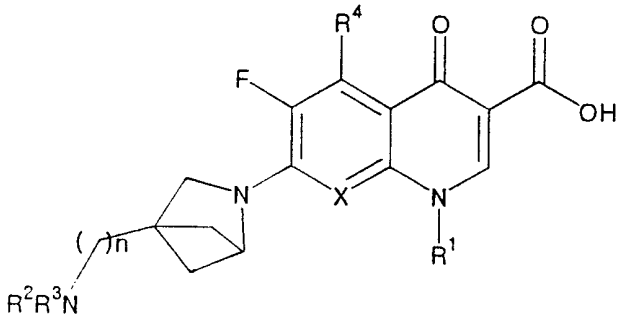
1-(2-fluoroethyl)-6,8-difluoro-7-(1-aminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-5-amino-6,8-difluoro-7-(1-amino-3-azabicyclo-[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

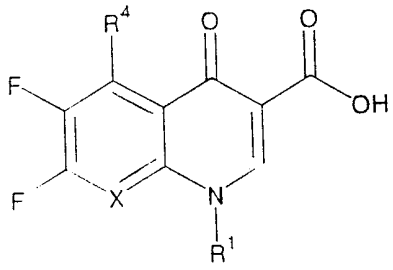
1-cyclopropyl-6-fluoro-8-methoxy-7-(1-N-(2-fluoroethyl)amino-methyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

1-cyclopropyl-6-fluoro-8-chloro-7-(1-N-methylaminomethyl-3-azabicyclo[2.1.1]hex-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid; and pharmaceutically acceptable salts thereof.

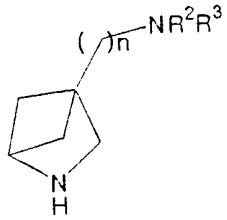
4. A process for preparing a quinolone carboxylic acid derivative of formula(I), which comprises reacting a compound of formula(II) with a compound of formula(III) in a solvent in the presence of a base:



(I)



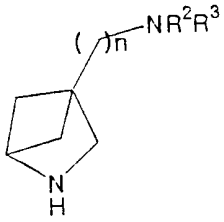
(II)



(III)

wherein R^1, R^2, R^3, R^4, X and n have the same meanings as defined in claim 1.

5. A compound of formula(III):



(III)

wherein, R^2, R^3 and n have the same meanings as defined in claim 1.

6. An antibacterial composition comprising an effective amount of the quinolone carboxylic acid derivative or a pharmaceutically acceptable salt thereof of claim 1 as an active ingredient, and a pharmaceutically acceptable carrier and/or adjuvant.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00246

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 487/08,401/14; A 61 K 31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 487/00,401/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 350 733 A2 (BAYER) 17 January 1990 (17.01.90), claims 1,4-6,8 (cited in the application).	1-4,6
A	US 5 631 266 A (KIM) 20 May 1997 (20.05.97), claims 1,3; tables 1,2,3; processes A,B (cited in the application).	1-4,6
A	Chemical Abstracts, Vol.124, No.19, 06 May 1996 (Columbus, Ohio, USA), page 1241, column 1, abstract No.260743v, STEVENS, C. et al.:"A New Entry into 2-Azabicyclo 2.1.1 hexanes via 3-(Chloromethyl)= cyclobutanone", & J. Org. Chem. 1996, 61(6), 2174-8.	1,5
A	Chemical Abstracts, Vol.109, No.1, 04 July 1988 (Columbus, Ohio, USA), page 600, column 1, abstract No.6335d, LEE, Y.B.:"Rearrangement, cycloaddition and heteroatom insertion routes to bridged N and O heterocycles. I. Preparation and bromination of 2-= azabicyclo[2.2.0]hex-5-enes. Route to 2-azabicyclo= [2.1.1]hexanes. II. Electronic and steric effects in	5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998 (12.10.98)	20 October 1998 (20.10.98)
Name and mailing address of the ISA/ Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Weniger Telephone No. 1/53424/341

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00246

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	intramolecular cycloaddition of 2-(3-butenyl)-1,2-= dihydropyridines. III. O and N insertion reactions. Bicyclo[2.2.1]heptan-2-ones", & Diss. Abstr. Int. B 1987, 48(4), 1051. ----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00246

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A2 350733	17-01-90	DE A1 3906365	18-01-90
		AT E 135354	15-03-96
		AU A1 36594/89	15-03-90
		AU B2 616277	24-10-91
		AU A1 10283/92	27-02-92
		AU A1 25286/92	26-11-92
		AU A1 60557/94	09-06-94
		AU B2 650316	16-06-94
		AU A1 72991/94	08-12-94
		AU B2 658667	27-04-95
		AU B2 668287	26-04-96
		AU B2 671386	22-08-96
		CN A 1039589	14-02-90
		CN B 1027165	28-12-94
		CN A 1097759	25-01-95
		CN A 1143080	19-02-97
		CN B 1036005	01-10-97
		DE C0 58909622	25-09-97
		DK A0 3500/89	14-07-89
		DK A 3500/89	16-01-90
		DK B1 170404	21-08-95
		EP A3 350733	27-12-90
		EP B1 350733	13-03-96
		EP A1 757990	12-02-97
		EP B1 757990	20-08-97
		ES T3 2109219	16-01-98
		FI A0 893403	13-07-89
		FI A 893403	16-01-90
		FI B 94251	28-04-95
		FI C 94251	10-08-95
		GR T3 3024841	30-01-98
		HU A2 52087	28-06-90
		HU A0 9301002	28-06-93
		HU B 209130	30-08-93
		HU A2 65936	29-08-94
		HU A3 9500442	28-09-95
		HU B3 211472	28-11-95
		IL A0 90940	09-02-90
		IL A1 90940	12-04-94
		JP A2 2069474	08-03-90
		JP B2 2771853	02-07-98
		JP A2 10182600	07-07-98
		NO A0 892715	29-06-89
		NO A 892715	16-01-90
		NO B 168889	06-01-92
		NO C 168889	15-04-92
		NZ A 229914	24-03-92
		NZ A 239485	26-03-96
		PT A 91165	08-02-90
		PT B 91165	01-03-95
		US A 4990517	05-02-91
		US A 5059597	22-10-91
		US A 5416096	16-05-95
		US A 5607942	04-03-97
		AU A1 60556/94	09-06-94
		AU B2 668286	26-04-96
		DD A5 285601	19-12-90
		HU B 213099	28-02-97
		PH A 26723	15-09-92
		ZA A 8905366	25-04-90
		DE A1 3906358	12-04-90
US A 5631266	20-05-97	US A 5498615	12-03-96
		AU A1 42727/93	21-11-94
		CN A 1094405	02-11-94
		EP A1 622367	02-11-94
		WO A1 9425464	10-11-94
		ZA A 9302944	01-11-93