

AUSTRALIA

623757 CONVENTION

Patents Act

APPLICATION FOR A STANDARD PATENT

Wakunaga Seiyaku Kabushiki Kaisha
3-1-39, Fukushima, Fukushima-ku, Osaka-shi, Osaka-fu, JAPAN

hereby applies for the grant of a standard patent for an invention entitled:

**NOVEL QUINOLONE DERIVATIVES, PREPARATION PROCESSES THEREOF, AND
ANTIBACTERIAL AGENTS CONTAINING THE SAME**

which is described in the accompanying complete specification.

Details of basic application(s):-

82321/1989 JAPAN
238064/1989 JAPAN

31 March 1989
13 September 1989

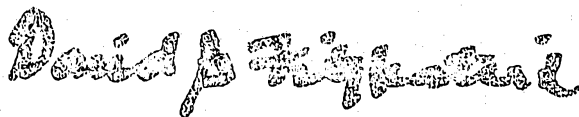
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DATED this TWENTY EIGHTH day of MARCH 1990

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
Wakunaga Seiyaku Kabushiki Kaisha

By:



Our Ref : 167387
POF Code: 1544/114851

M 014532 230390

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

(h) Insert country, filing date, and basic applicant(s) for the/each basic application

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

In support of the (a) Convention application made by

(b) WAKUNAGA SEIYAKU KABUSHIKI KAISHA

(hereinafter called "applicant(s)" for a patent (c)

for an

invention entitled (d)

NOVEL QUINOLONE DERIVATIVES, PREPARATION PROCESSES THEREOF, AND ANTIBACTERIAL AGENTS CONTAINING THE SAME

I/~~WE~~ (e) Gisuke WAKUNAGA of c/o WAKUNAGA SEIYAKU KABUSHIKI KAISHA, 3-1-39, Fukushima, Fukushima-ku, Osaka-shi, Osaka-fu, Japan

do solemnly and sincerely declare as follows:

~~I am/we are the applicant(s).~~

(or, in the case of an application by a body corporate)

1. I am/~~WE~~ are authorized to make this declaration on behalf of the applicant(s).

~~I am/we are the actual inventor(s) of the invention.~~

(or, where the applicant(s) is/are not the actual inventor(s))

2. (f) Yasuhiro KURAMOTO, Masayasu OKUHIRA and Takashi YATSUNAMI whose addresses are all c/o WAKUNAGA SEIYAKU KABUSHIKI KAISHA, 1624, Shimo Kotachi, Koda-cho, Takata-gun, Hiroshima-ken, Japan

~~is/are~~ are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:

(g)

The applicant is the assignee of the actual inventors.

(Note: Paragraphs 3 and 4 apply **only** to Convention applications)

3. The basic application(s) for patent or similar protection on which the application is based is/~~are~~ identified by **country, filing date, and basic applicant(s)** as follows:

(h) (1) Japan, March 31, 1989, WAKUNAGA SEIYAKU KABUSHIKI KAISHA
(2) Japan, September 13, 1989, WAKUNAGA SEIYAKU KABUSHIKI KAISHA

4. The basic application(s) referred to in paragraph 3 hereof ~~was/were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at (k) Osaka, Japan

Dated (l) April 10, 1990

(m)

Gisuke WAKUNAGA, President
WAKUNAGA SEIYAKU KABUSHIKI KAISHA

To: The Commissioner of Patents

P18/7/81

PHILLIPS ORMONDE & FITZPATRICK

Patent and Trade Mark Attorneys

367 Collins Street

Melbourne, Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-52281/90
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 623757

(54) Title
 NOVEL QUINOLONE DERIVATIVES, PREPARATION PROCESSES THEREOF, AND ANTIBACTERIAL AGENTS CONTAINING THE SAME

International Patent Classification(s)
 (51)⁵ C07D 405/04 A01N 043/40 A01N 043/42 A01N 043/44
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 A61K 031/47 A61K 031/54 C07D 401/04 C07D 401/14
 C07D 405/14 C07D 409/04 C07D 409/14 C07D 413/14
 C07D 471/04 C07D 487/04 C07D 487/08 C07D 498/04
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(21) Application No. : 52281/90

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1-238064	13.09.89	JP JAPAN

(43) Publication Date : 04.10.90

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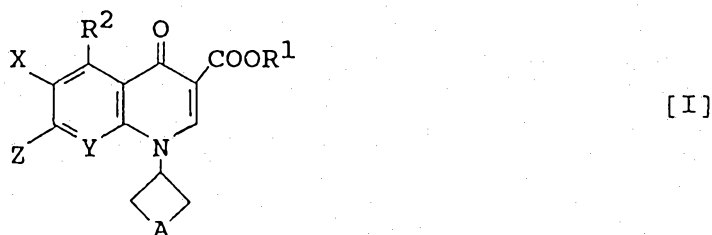
(71) Applicant(s)
 WAKUNAGA SEIYAKU KABUSHIKI KAISHA

(72) Inventor(s)
 TAKASHI YATSUNAMI; MASAYASU OKUHIRA; YASUHIRO KURAMOTO

(74) Attorney or Agent
 PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, MELBOURNE VIC 3000

(57) Claim

1. A quinolone derivative represented by the following formula [I] or a salt thereof:



wherein R¹ means a hydrogen atom or a carboxyl-protecting group; R² denotes a hydrogen or halogen atom or a hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)amino group; A represents an oxygen or sulfur atom or N-R³ in which R³ is a hydrogen atom or an amino-protecting group; X is a hydrogen or halogen atom; Y means a nitrogen atom or C-R⁴ in which R⁴ is a hydrogen or halogen atom or a lower alkyl or lower alkoxyl group; and Z denotes a halogen atom or a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom.

(11) AU-B-52281/90
(10) 623757

-2-

18. An antibacterial agent comprising as an active ingredient the quinolone derivative or the salt thereof according to claim 1 and a pharmaceutically acceptable carrier.

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6 2 3 7 5 7

Class

- 1 -

TITLE OF THE INVENTION:

NOVEL QUINOLONE DERIVATIVES, PREPARATION PROCESSES
THEREOF, AND ANTIBACTERIAL AGENTS CONTAINING THE SAME

5

BACKGROUND OF THE INVENTION

1) Field of the Invention:

The present invention relates to novel quinolone derivatives and salts thereof, said derivatives and salts having excellent antibacterial activities, to preparation
10 processes thereof and also to antibacterial agents containing the same.

2) Description of the Related Art:

New quinolone agents having pyridonecarboxylic acid as a basic skeleton have excellent antibacterial activities and
15 a broad antibacterial spectrum, so that they have attracted interests as synthetic antibacterial agents comparable with antibiotics. Among these, norfloxacin [Japanese Patent Application Laid-Open (Kokai) No. 141286/1978], enoxacin [Japanese Patent Application Laid-Open (Kokai) No.
20 31042/1980], ofloxacin [Japanese Patent Application Laid-Open (Kokai) No. 46986/1982], ciprofloxacin [Japanese Patent Application Laid-Open (Kokai) No. 76667/1983] and the like have already found wide-spread clinical utility as therapeutic agents for infectious diseases.

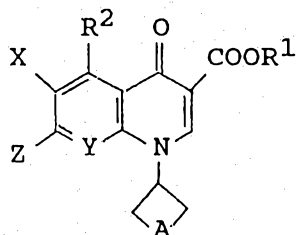
25 The new quinolone agents known to date are however not

fully satisfactory either in antibacterial activities, oral absorption, long-acting property, side effects on central nervous system, etc. To solve these problems, investigations are now under way, especially on substituents on positions 1, 5, 6, 7 and 8 of the quinoline and naphthylidine skeletons.

SUMMARY OF THE INVENTION

With the foregoing in view, the present inventors have conducted an extensive investigation with a view toward providing clinically excellent synthetic antibacterial agents improved in the problems described above. As a result, it has been found that quinolone derivatives which have the quinoline or naphthylidine skeleton with an oxetane, thietane or azetidine ring introduced on position 1 thereof and are represented by the formula [I] to be described herein, have strong antibacterial activities against gram-negative and gram-positive bacteria and also a suitable hydrophilicity/hydrophobicity balance required for synthetic antibacterial agents, leading to the completion of the present invention.

The present invention therefore provides quinolone derivatives represented by the below-described formula [I] and salts thereof, their preparation processes and antibacterial agents containing them.



[I]

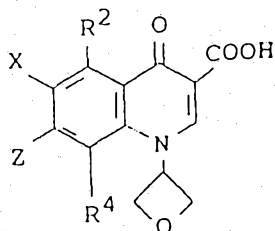
5 wherein R¹ means a hydrogen atom or a carboxyl-protecting group; R² denotes a hydrogen or halogen atom or a hydroxyl, lower alkoxy, amino, aralkylamino, or mono- or di-(lower
10 alkoxy)amino group; A represents an oxygen or sulfur atom or N-R³ in which R³ is a hydrogen atom or an amino-protecting group; X is a hydrogen or halogen atom; Y means a nitrogen atom or C-R⁴ in which R⁴ is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group; and Z denotes a halogen atom or a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom.

15 ~~In the present invention, the term "lower" employed in the definition for some substituent groups in formula [I] means that the group referred to has 1-7, preferably 1-4 carbon atoms when the substituent group is a linear or branched group but has 3-7 carbon atoms when the substituent
20 group is a cyclic group.~~

The compounds [I] and their salts according to the present invention are extremely valuable as antibacterial agents. They can therefore be used as drugs for human being and animals and also as drugs for fish diseases, agricultural
25 ~~chemicals and feed preservatives.~~

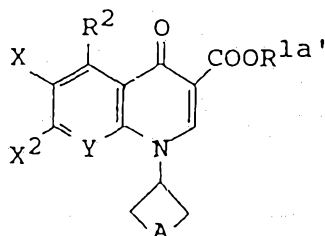


The present invention also provides a quinolone derivative represented by the following formula or a salt thereof:

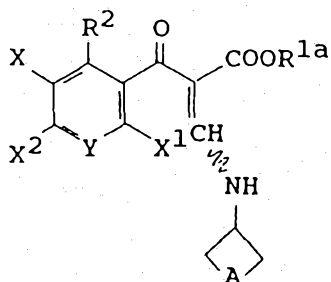


wherein R^2 denotes a hydrogen or an amino group, X is a halogen atom, R^4 is a hydrogen or halogen atom and Z is a substituted or unsubstituted saturated 4-6 membered heterocyclic group having at least one nitrogen atom as a hetero atom.

The present invention further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:

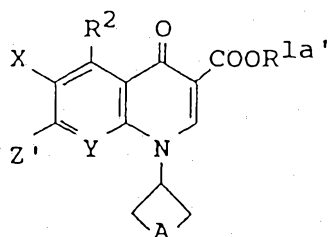


wherein $R^{1a'}$ means a hydrogen atom or a lower alkyl group; R^2 denotes a hydrogen or halogen atom or a hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)-amino group; A represents an oxygen or sulfur atom or $N-R^3$ in which R^3 is a hydrogen atom or an amino-protecting group; X is a hydrogen or halogen atom; X^2 means a halogen atom; and Y means a nitrogen atom or $C-R^4$ in which R^4 is a hydrogen or halogen atom or a lower alkyl or lower alkoxyl group, which comprises cyclizing a compound represented by the following formula:



wherein R^{1a} means a lower alkyl group; X^1 denotes a halogen atom; and R^2 , A, X, X^2 and Y have the same meanings as defined above; and optionally removing the ester residual group and/or amino-protecting group; and when the salt is desired, converting the thus-cyclized product into the salt by a method known *per se* in the art.

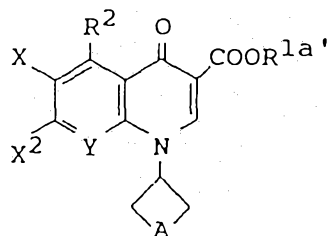
The present invention further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:



wherein $R^{1a'}$ means a hydrogen atom or a lower alkyl group; R^2 denotes a hydrogen or halogen atom or a hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)-amino group; A represents an oxygen or sulfur atom or $N-R^3$ in which R^3 is a hydrogen atom or an amino-protecting group; X is a hydrogen or halogen atom; Y means a nitrogen atom or $C-R^4$ in which R^4 is a hydrogen or halogen atom or a lower alkyl or lower alkoxyl group; and Z' is a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:

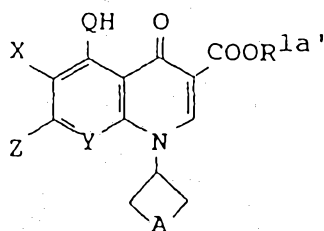


wherein Z' has the same meaning as defined above, with a compound represented by the following formula:



wherein X² denotes a halogen atom; and R^{1a'}, R², A, X and Y have the same meanings as defined above; and optionally removing the ester residual group and/or amino-protecting group; and when the salt is desired, converting the reaction product into the salt by a method known *per se* in the art.

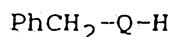
The present invention still further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:



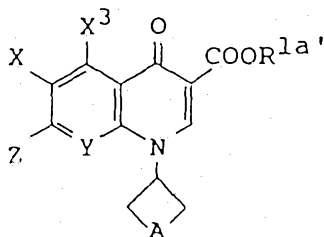
wherein R^{1a'} means a hydrogen atom or a lower alkyl group; A represents an oxygen or sulfur atom or N-R³ in which R³ is a hydrogen atom or an amino-protecting group; Q represents -O-, -NH- or -NR¹⁶- in which R¹⁶ is a lower alkyl group; X is a hydrogen or halogen atom; Y means a nitrogen atom or C-R⁴ in which R⁴ is a hydrogen or halogen atom or a lower alkyl or



lower alkoxyl group; and Z is a halogen atom or a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:



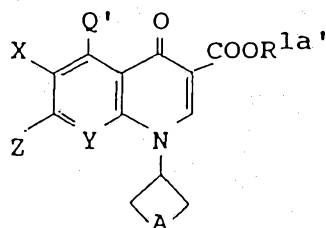
5 wherein Q has the same meaning as defined above, with a compound represented by the following formula:



wherein X³ denotes a halogen atom; and R^{1a}, A, X, Y and Z have the same meanings as defined above; removing the benzyl group from the reaction product thus formed; and optionally removing the ester residual group and/or amino-protecting group; and when the salt is desired, converting the resultant benzyl-free product into the salt by a method known *per se* in the art.

15 The present invention still further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:

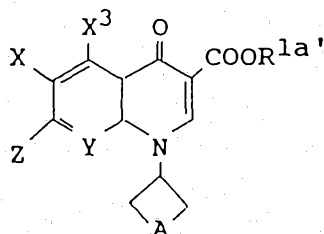




wherein $R^{1a'}$ means a hydrogen atom or a lower alkyl group; A represents an oxygen or sulfur atom or $N-R^3$ in which R^3 is a hydrogen atom or an amino-protecting group; Q' represents a hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)amino group; X is a hydrogen or halogen atom; Y means a nitrogen atom or $C-R^4$ in which R^4 is a hydrogen or halogen atom or a lower alkyl or lower alkoxyl group; and Z is a halogen atom or a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:



wherein Q' has the same meaning as defined above, with a compound represented by the following formula:

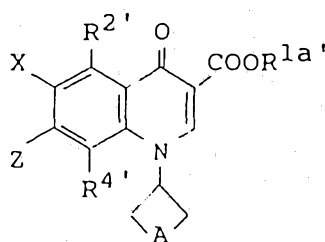


wherein X^3 denotes a halogen atom; and $R^{1a'}$, A, X, Y and Z have the same meanings as defined above; and optionally

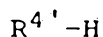


removing the ester residual group and/or amino-protecting group; and when the salt is desired, converting the resultant product into the salt by a method known *per se* in the art.

5 The present invention yet still further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:



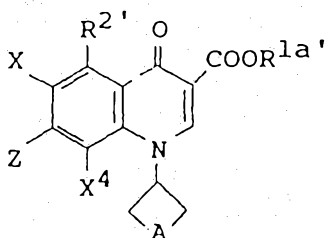
wherein R^{1a'} means a hydrogen atom or a lower alkyl group; R^{2'} denotes a hydrogen atom or a hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)amino group; R^{4'} represents a lower alkoxyl group; A denotes an oxygen or sulfur atom or N-R³ in which R³ is a hydrogen atom or an amino-protecting group; X means a hydrogen or halogen atom; and Z is a halogen atom or a substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:



wherein R^{4'} has the same meaning as defined above, with a compound represented by the following formula:

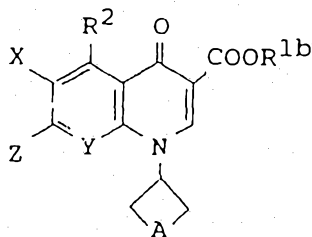
20





wherein X^4 denotes a halogen atom; and $R^{1a'}$, $R^{2'}$, A, X and Z have the same meanings as defined above; and optionally removing the ester residual group and/or amino-protecting group; and when the salt is desired, converting the reaction product into the salt by a method known *per se* in the art.

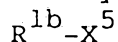
The present invention still further provides a process for the preparation of a quinolone derivative represented by the following formula or a salt thereof:



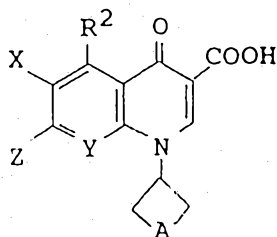
wherein R^{1b} means a carboxyl-protecting group; R^2 denotes a hydrogen or halogen atom or a hydroxyl, lower alkoxy, amino, aralkylamino, or mono- or di-(lower alkyl)amino group; A represents an oxygen or sulfur atom or $N-R^3$ in which R^3 is a hydrogen atom or an amino-protecting group; X is a hydrogen or halogen atom; Y means a nitrogen atom or $C-R^4$ in which R^4 is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group; and Z is a halogen atom or a



substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:



wherein X^5 means a halogen atom and R^{1b} has the same meaning as defined above, with a compound represented by the following formula:



wherein R^2 , X, Y and Z have the same meanings as defined above; and when the salt is desired, converting the reaction product into the salt by a method known per se in the art.

The present invention still further provides an antibacterial agent comprising as an active ingredient the quinolone derivative or the salt thereof as described above and a pharmaceutically acceptable carrier.

The present invention still further provides a method of inhibiting bacterial growth comprising administering to a patient in need an effective amount of an antibacterial agent as described above.

In the present invention, the term "lower" employed in the definition for some substituent groups in formula [I] means that the group referred to has 1-7, preferably 1-4 carbon atoms when the substituent group is a linear or branched group but has 3-7 carbon atoms when the substituent group is a cyclic group.

The compounds [I] and their salts according to the present invention are extremely valuable as antibacterial agents. They can therefore be used as drugs for human being and animals and also as drugs for fish diseases, agricultural chemicals and food preservatives.

DETAILED DESCRIPTION OF THE INVENTION

AND PREFERRED EMBODIMENTS

The term "carboxyl-protecting group" represented by R^1 indicates the ester residual group of a carboxylate ester and means a desired group capable of undergoing a relatively easy cleavage and yielding a corresponding free carboxyl group. Specific examples of the carboxyl-protecting group includes those removable upon treatment under mild conditions, such as hydrolysis or catalytic reduction, such as lower alkyl groups (e.g., methyl, ethyl, n-propyl, t-butyl, etc.), aralkyl groups (e.g., benzyl, etc.), and aryl groups (e.g., phenyl, etc.); and those readily removable *in vivo*, such as lower alkanoyloxy-lower alkyl groups (e.g., acetoxy-methyl, pivaloyloxymethyl, etc.), lower alkoxycarbonyloxy-lower alkyl groups (e.g., methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, etc.), lower alkoxymethyl groups (e.g., methoxymethyl, etc.), lactonyl groups (phthalidyl, etc.), di(lower alkyl)amino-lower alkyl groups (e.g., 1-dimethylaminoethyl, etc.), (5-methyl-2-oxol-4-yl)methyl group, and the like.

Illustrative of the halogen atom represented by R^2 include F, Cl and Br, with F and Cl being preferred. Examples of the lower alkoxyl group indicated by R^2 include methoxy, ethoxy and isopropoxy. Examples of the mono- or di-(lower alkyl)amino group include methylamino, ethylamino or

dimethylamino. Examples of the aralkyl group represented by R^2 include benzyl and phenethyl.

When A is the group $N-R^3$, illustrative of the amino-protecting group denoted by R^3 include lower alkyl groups, 5 lower alkenyl groups and the like as well as those employed as amino-protecting groups in usual peptide syntheses. More specific examples of the amino-protecting group include alkyloxycarbonyl groups (ethoxycarbonyl, t-butoxycarbonyl, etc.), acyl groups (acetyl, benzoyl, etc.), benzyl-type pro- 10 tecting groups (benzyl, benzhydryl, etc.), and the like. In addition, illustrative of the lower alkyl group include linear or branched alkyl groups having 1-7, preferably 1-4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl and t-butyl. Examples of the lower alkenyl group include linear 15 and branched alkenyl groups having 2-7, preferably 2-5 carbon atoms, such as vinyl, allyl and 1-propenyl.

Exemplary halogen atoms represented by X include those mentioned above as R^2 , with F and Cl being preferred. Of these, F is more preferred.

20 When Y is $C-R^4$, illustrative of the halogen atom represented by R^4 include F, Cl and Br, with F and Cl being preferred. Illustrative of the lower alkyl group indicated by R^4 include linear or branched alkyl groups having 1-7, preferably 1-4 carbon atoms, such as methyl, ethyl, n- 25 propyl, isopropyl and t-butyl, with methyl being preferred.

Exemplary lower alkoxy groups represented by R^4 include those mentioned above as R^2 , with methoxy being preferred.

Exemplary halogen atoms represented by Z include those mentioned above as R^2 , with F and Cl being preferred.

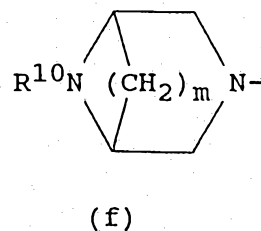
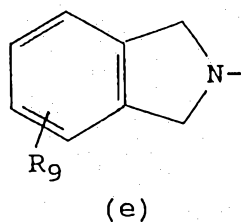
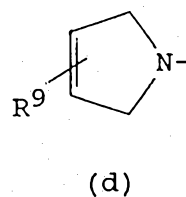
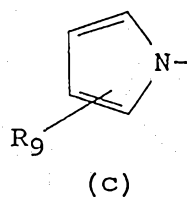
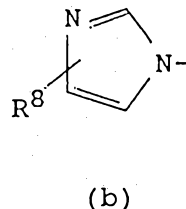
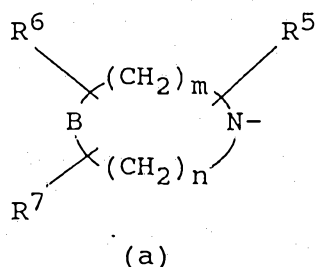
- 5 Further, the heterocyclic group represented by Z and containing at least one nitrogen atom as a hetero atom may be either a saturated heterocyclic group or an unsaturated heterocyclic group. It may be fused with another heterocyclic ring containing at least one nitrogen atom or with a
- 10 benzene ring. Illustrative of the heterocyclic ring include heterocyclic groups containing 1-3 nitrogen atoms, such as residual groups of azetidine, pyrrolidine, pyrroline, pyrrole, imidazole, pyrazole, pyrazolidine, pyridine, pyrimidine, piperidine, piperazine, homopiperazine and triazole;
- 15 heterocyclic groups containing as hetero atoms one nitrogen atom and another hetero atom selected from oxygen atom and sulfur atom, such as residual groups of thiazolidine, thiazole, morpholine and thiomorpholine; heterocyclic groups containing another heterocyclic ring or a benzene ring fused
- 20 therewith, such as residual groups of indole, dihydroindole, isoindole, dihydroisoindole, isoindoline, naphthylidene, perhydronaphthylidene, pyrrolidino[1,2-a]piperazine, pyrrolidino[3,4-c]pyrrolidine and pyrrolidino[3,4-b]morpholine; and bicyclic heterocyclic groups such as residual groups of
- 25 2,5-diazabicyclo[2,2,1]heptane and 2,5-diazabicyclo[3,1,1]-

heptane.

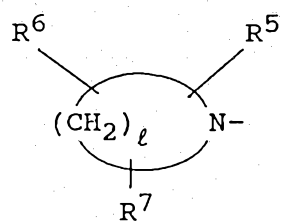
Preferably, these heterocyclic groups are residual groups of 3-7 membered rings and the heterocyclic groups containing another heterocyclic ring or a benzene ring fused therewith are residual groups of 8-12 membered rings. They may be substituted with 1-4 suitable substituent groups. Exemplary substituent groups include nitro, hydroxyl and amino groups, halogen atoms, lower alkyl groups, cyclo-lower alkyl groups, lower alkoxy groups, mono- or di-(lower alkyl)amino groups, cyclo-lower alkylamino groups, amino-lower alkyl groups, halo-lower alkyl groups, mono- or di-(lower alkyl)amino-lower alkyl groups, hydroxy-lower alkyl groups, alkoxy-lower alkyl groups, cyclo(lower alkyl)amino-lower alkyl groups, substituted or unsubstituted acyloxy groups, lower alkylthio groups, substituted or unsubstituted aryl groups, cyano-lower alkyl groups, substituted or unsubstituted acylamino groups, substituted or unsubstituted alkoxycarbonylamino groups, substituted or unsubstituted alkoxycarbonyl groups, substituted or unsubstituted amino-(cyclo-lower alkyl) groups, substituted or unsubstituted acylamino-lower alkyl groups, substituted or unsubstituted alkoxycarbonylamino-lower alkyl groups, lower alkenyl groups, cyano group, mercapto group, formimidoyl group, lower alkylimidoyl groups, formimidoylamino group, lower alkylimidoylamino groups, substituted or unsubstituted

aralkyl groups or lower alkylidene groups, and mono- or di-(lower alkyl)hydrazino groups. These substituent groups may be bonded to on the same atom or different atoms in each heterocyclic group.

- 5 The heterocyclic group represented by Z and containing at least one nitrogen atom as a hetero atom may be bonded to the quinolone skeleton at any one of the ring-forming atoms thereof. Preferred examples include the following heterocyclic rings bonded to the quinolone skeleton at a nitrogen
- 10 atom thereof:

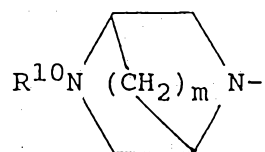


5

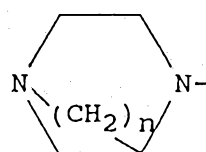


(g)

10

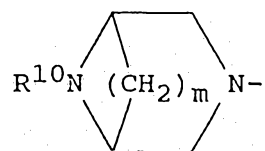


(h)

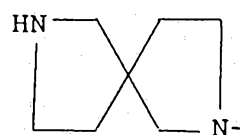


(i)

15

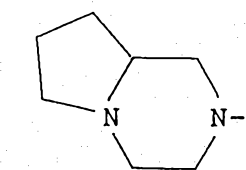


(j)

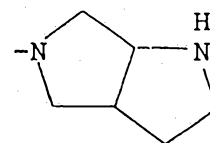


(k)

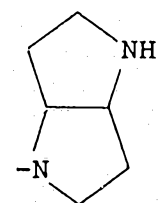
20



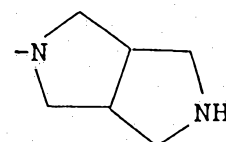
(l)



(m)

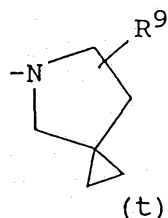
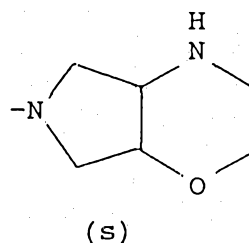
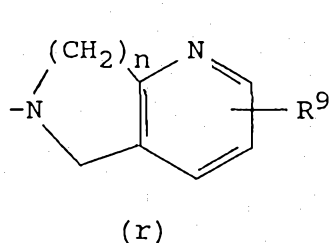
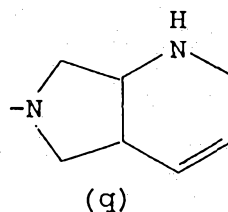
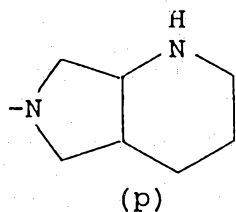


(n)



(o)

25



15 wherein B means an oxygen atom, a sulfur atom, $\text{-NR}^{10}\text{-}$ or
 $\text{-}\overset{\text{O}}{\parallel}\text{C-N-}$; R^5 , R^6 and R^7 may be the same or different and
individually denote a hydrogen or halogen atom or a
hydroxyl, amino, lower alkyl, halo-lower alkyl, substituted
20 or unsubstituted mono- or di-(lower alkyl)amino, cyclo(lower
alkyl)amino, amino-lower alkyl, substituted or unsubstituted
mono- or di(lower alkyl)amino-lower alkyl, cyclo(lower
alkyl)amino-lower alkyl, substituted or unsubstituted
alkoxyl, substituted or unsubstituted acyloxy, lower
25 alkylthio, substituted or unsubstituted aryl, cyano-lower

alkyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted amino(cyclo-lower alkyl), substituted or unsubstituted acylamino-lower alkyl, substituted or unsubstituted alkoxycarbonylamino-lower alkyl, hydroxy-lower alkyl, substituted or unsubstituted alkoxy-lower alkyl, lower alkenyl, cyano, mercapto, formimidoylamino, or lower alkylimidoylamino group, R^8 represents a hydrogen atom or a lower alkyl group, R^9 is a hydrogen or halogen atom or a nitro, substituted or unsubstituted lower alkyl, amino, amino-lower alkyl, mono- or di-(lower alkyl)amino-lower alkyl, lower alkoxy, hydroxyl, substituted or unsubstituted mono- or di-(lower alkyl)amino, formimidoylamino, or a lower alkylimidoylamino group, R^{10} means a hydrogen atom or a substituted or unsubstituted lower alkyl, substituted or unsubstituted cyclo-lower alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted acyl, substituted or unsubstituted alkoxycarbonyl, hydroxy-lower alkyl, formimidoyl, or lower alkylimidoyl group, m stands for 1, 2 or 3, n denotes 1 or 2, and ℓ is 3, 4 or 5.

As R^5 , R^6 and R^7 , may be mentioned, for example, halogen atoms (e.g., F, Cl, etc.), hydroxyl, amino, substituted or unsubstituted mono- or di(lower alkyl)amino groups (e.g., methylamino, ethylamino, n-propylamino,

dimethylamino, diethylamino, benzylamino, benzylethylamino, benzylamino, benzylethylamino, pyrrolidinyl, piperidinyl, hydroxyethylamino, methoxyethylamino, fluoroethylamino, etc.), cyclo(lower alkyl)amino groups (e.g., cyclopropyl-
5 amino, cyclopentylamino, etc.), lower alkyl groups (e.g., methyl, ethyl, n-propyl, etc.), halo-lower alkyl groups (e.g., fluoromethyl, trifluoromethyl, etc.), amino-lower alkyl groups (e.g., aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-amino-1-methylethyl, etc.), substituted or unsubstituted
10 mono- or di(lower alkyl)amino-lower alkyl groups (e.g., methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, n-propylmethylaminomethyl, di(n-propyl)-aminomethyl, isopropylaminomethyl, methylaminoethyl, dimethylaminoethyl, methylamino-n-propyl, diethylaminoethyl,
15 dimethylamino-n-propyl, pyrrolidinylmethyl, benzylamino-methyl, benzylmethylaminomethyl, 2-fluoroethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethylaminomethyl, etc.), cyclo(lower alkyl)amino-lower alkyl groups (e.g., cyclopropylaminomethyl, etc.), sub-
stituted or unsubstituted alkoxyl groups (e.g., methoxy, ethoxy, n-propoxy, phenoxy, p-chlorophenoxy, p-fluoro-
20 phenoxy, benzyloxy, etc.), substituted or unsubstituted acyloxy groups (e.g., acetoxy, benzoyloxy, etc.), lower alkylthio groups (e.g., methylthio, ethylthio, etc.), sub-
25 stituted or unsubstituted aryl groups (e.g., phenyl, p-

fluorophenyl, p-methoxyphenyl, etc.), cyano-lower alkyl groups (e.g., cyanomethyl), substituted or unsubstituted alkoxy-carbonylamino groups (e.g., t-butoxycarbonylamino, etc.), substituted or unsubstituted acylamino groups (e.g., acetylamino, benzoylamino, ~~acetyl, benzoyl~~, etc.), substituted or unsubstituted alkoxy-carbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, etc.), substituted or unsubstituted aminocyclo-lower alkyl groups (e.g., 1-aminocyclopropyl, etc.), substituted or unsubstituted acylamino-lower alkyl groups (e.g., acetyl-aminoethyl, ~~amino~~, etc.), substituted or unsubstituted alkoxy-carbonyl-amino-lower alkyl groups (e.g., t-butoxycarbonylaminomethyl, benzyloxycarbonylaminomethyl, etc.), hydroxy-lower alkyl groups (e.g., hydroxymethyl, etc.), substituted or unsubstituted alkoxy-lower alkyl groups (e.g., methoxymethyl, etc.), lower alkenyl groups (e.g., vinyl, allyl, etc.), lower alkylidene groups (e.g., methylene, ethylidene, etc.), cyano, mercapto, formimidoyl, lower alkylimidoyl groups (e.g., acetimidoyl, etc.), formimidoylamino, lower alkylimidoylamino groups (e.g., acetimidoylamino, etc.), mono- or di-(lower alkyl)hydrazino groups (e.g., 2-methylhydrazino, etc.) and the like.

As described above, R^{10} represents a hydrogen atom, a substituted or unsubstituted alkyl group, substituted or unsubstituted cyclo-lower alkyl group, substituted or unsubstituted aralkyl group, substituted or unsubstituted aryl



group, substituted or unsubstituted alkenyl group, substituted or unsubstituted acyl group, substituted or unsubstituted alkoxycarbonyl group, hydroxy-lower alkyl group, formimidoyl group, or lower alkylimidoyl group. Typical examples of R^{10} are as follows. Illustrative of the lower alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl and t-butyl. Exemplary cyclo-lower alkyl groups include cyclopropyl, cyclopentyl and cyclohexyl. Examples of the aralkyl group include benzyl, phenylethyl and phenylpropyl. Exemplary aryl groups include phenyl. Illustrative of the lower alkenyl group include allyl, 2-butenyl, 3-methyl-2-butenyl and 3-butenyl. These groups may be substituted by 1-3 substituents selected from the class consisting of halogen atoms (e.g., F, Cl, etc.), hydroxy, substituted or unsubstituted amino groups (e.g., amino, methylamino, dimethylamino, ethylamino, acetamido, ethoxycarbonylamino, etc.), substituted or unsubstituted alkoxyl groups (e.g., methoxy, ethoxy, phenoxy, benzyloxy, p-bromobenzyloxy, etc.), lower alkyl groups (e.g., methyl, ethyl), carboxy, lower alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, etc.), cyano, lower alkylthio groups (e.g., methylthio), substituted or unsubstituted phenyl groups (e.g., phenyl, p-fluorophenyl, p-methoxyphenyl, etc.), substituted or unsubstituted acyl groups (e.g., formyl, acetyl, n-propionyl, benzoyl, etc.), and the

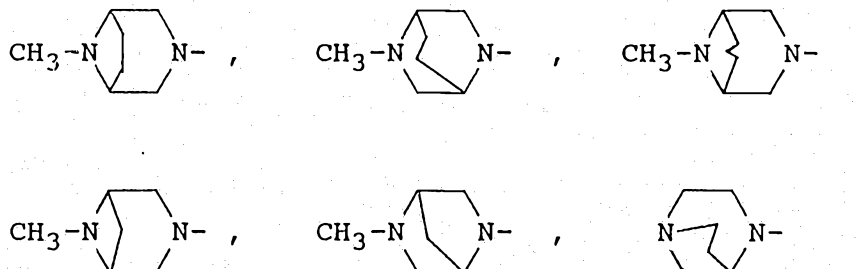
like.

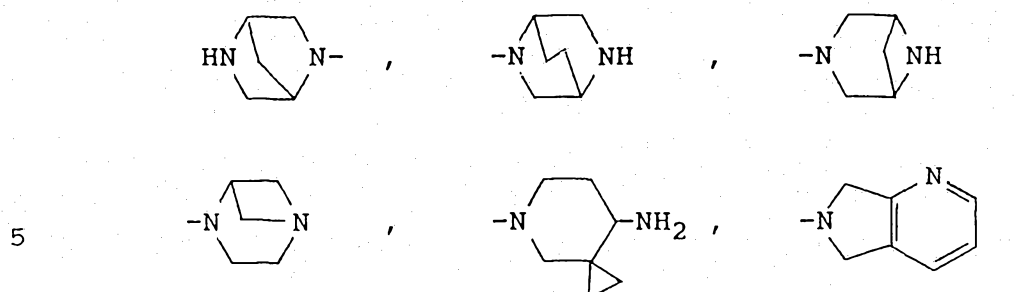
Exemplary lower alkyl groups represented by R^8 include methyl, ethyl, n-propyl, isopropyl and t-butyl.

Exemplary substituted or unsubstituted lower alkyl groups represented by R^9 include methyl, ethyl, aminomethyl, methylaminomethyl, dimethylaminomethyl, ethylaminomethyl and hydroxymethyl. Illustrative examples of the substituted or unsubstituted mono- or di-(lower alkyl)amino group also represented by R^9 include methylamino, ethylamino and dimethylamino.

Illustrative of the heterocyclic group of the formula (a) include piperazinyl, morpholino, thiomorpholino, homopiperazinyl, thiazolidinyl, oxazolidinyl and 3-oxo-1-piperazinyl.

Illustrative of the bicyclic heterocyclic groups represented by the formulae (f), (h)-(j), (r) and (t) include the following groups:





Exemplary heterocyclic groups represented by the formula (g) include residual groups of azetidine, pyrrolidine and piperidine.

10 Preferred specific examples of the heterocyclic group designated by the formulae (a) and (g) are as follows:

3-hydroxyazetidiny, 3-aminoazetidiny, 2-(N-t-butoxycarbonylamino)azetidiny, 3-acetylaminoazetidiny, 3-methylaminoazetidiny, 3-dimethylaminoazetidiny, 3-aminomethyl-

15 azetidiny, pyrrolidiny, 3-hydroxypyrrolidiny, 3,4-dihydroxypyrrolidiny, 3-methoxypyrrolidiny, 3-methylpyrrolidiny, 3-hydroxy-4-methylpyrrolidiny, 3-aminopyrrolidiny, 3-methylaminopyrrolidiny, 3-dimethylaminopyrrolidiny, 3-ethylaminopyrrolidiny, 3-diethylaminopyrrolidiny, 3-acetylamino-

20 pyrrolidiny, 3-t-butoxycarbonylaminopyrrolidiny, 3-(N-acetyl)methylaminopyrrolidiny, 3-(t-butoxycarbonyl)methylaminopyrrolidiny, 3-aminomethylpyrrolidiny, 3-methylaminomethylpyrrolidiny, 3-dimethylaminomethylpyrrolidiny, 3-ethylaminomethylpyrrolidiny, 3-

25 diethylaminomethylpyrrolidiny, 3-(N-acetyl)aminomethyl-

pyrrolidinyl, 3-(t-butoxycarbonyl)aminomethylpyrrolidinyl,
3-(N-acetyl)methylaminomethylpyrrolidinyl, 3-(t-butoxy-
carbonyl)methylaminomethylpyrrolidinyl, 3-(1-aminoethyl)-
pyrrolidinyl, 3-(2-aminoethyl)pyrrolidinyl, 3-(1-amino-1-
5 methylethyl)pyrrolidinyl, 3-(1-methylaminoethyl)pyrroli-
dinyl, 3-(1-dimethylaminoethyl)pyrrolidinyl, 3-amino-4-
methylpyrrolidinyl, 3-amino-5-methylpyrrolidinyl, 3-
methylamino-4-methylpyrrolidinyl, 3-dimethylamino-4-
methylpyrrolidinyl, 3-ethylamino-4-methylpyrrolidinyl, 3-
10 diethylamino-3-methylpyrrolidinyl, 3-diethylamino-4-
methylpyrrolidinyl, 3-aminomethyl-4-methylpyrrolidinyl, 3-
methylaminomethyl-4-methylpyrrolidinyl, 3-dimethylamino-
methyl-4-methylpyrrolidinyl, 3-ethylaminomethyl-4-methyl-
pyrrolidinyl, 3-(1-aminoethyl)-4-methylpyrrolidinyl, 3-(2-
15 aminoethyl)-4-methylpyrrolidinyl, 3-amino-4-ethylpyrroli-
dinyl, 3-methylamino-4-ethylpyrrolidinyl, 3-dimethylamino-4-
ethylpyrrolidinyl, 3-ethylamino-4-ethylpyrrolidinyl, 3-
diethylamino-4-ethylpyrrolidinyl, 3-aminomethyl-4-ethyl-
pyrrolidinyl, 3-methylaminomethyl-4-ethylpyrrolidinyl, 3-
20 dimethylaminomethyl-4-ethylpyrrolidinyl, 3-amino-3-methyl-
pyrrolidinyl, 3-methylamino-3-methylpyrrolidinyl, 3-
dimethylamino-3-methylpyrrolidinyl, 3-amino-3,4-dimethyl-
pyrrolidinyl, 3-amino-4,4-dimethylpyrrolidinyl, 3-amino-4,5-
dimethylpyrrolidinyl, 3-amino-2,4-dimethylpyrrolidinyl, 3-
25 methylamino-3,4-dimethylpyrrolidinyl, 2-methyl-3-amino-

pyrrolidinyl, 2-methyl-3-dimethylaminopyrrolidinyl, 3-amino-
4-vinylpyrrolidinyl, 3-amino-4-methoxypyrrolidinyl, 3-amino-
4-methoxymethylpyrrolidinyl, 3-methylamino-4-methoxy-
pyrrolidinyl, 3-dimethylamino-4-methoxypyrrolidinyl, 3-
5 ethylamino-4-methoxypyrrolidinyl, 3-diethylamino-4-methoxy-
pyrrolidinyl, 3-benzylamino-4-methoxypyrrolidinyl, 3-amino-
methyl-4-methoxypyrrolidinyl, 3-methylaminomethyl-4-methoxy-
pyrrolidinyl, 3-dimethylaminomethyl-4-methoxypyrrolidinyl,
3-ethylaminomethyl-4-methoxypyrrolidinyl, 3-aminomethyl-3-
10 methoxypyrrolidinyl, 3-methylaminomethyl-3-methoxy-
pyrrolidinyl, 3-dimethylaminomethyl-3-methoxypyrrolidinyl,
3-amino-4-ethoxypyrrolidinyl, 3-dimethylamino-4-ethoxy-
pyrrolidinyl, 3-methylamino-4-ethoxypyrrolidinyl, 3-amino-
methyl-4-ethoxypyrrolidinyl, 3-dimethylaminomethyl-4-ethoxy-
15 pyrrolidinyl, 3-amino-4-aminocarbonylpyrrolidinyl, 3-amino-
4-dimethylaminocarbonylpyrrolidinyl, 3-amino-4-hydroxy-
pyrrolidinyl, 3-amino-4-hydroxymethylpyrrolidinyl, 3-amino-
4-methyl-4-hydroxymethylpyrrolidinyl, 3-amino-4-hydroxy-
ethylpyrrolidinyl, 3-aminomethyl-4-hydroxypyrrolidinyl, 3-
20 dimethylaminomethyl-4-hydroxypyrrolidinyl, 3,4-dihydroxy-
pyrrolidinyl, 3,4-dimethoxypyrrolidinyl, 3-hydroxy-4-methyl-
pyrrolidinyl, 3-amino-4-fluoropyrrolidinyl, 3-amino-4-
fluoromethylpyrrolidinyl, 3-amino-4-trifluoromethyl-
pyrrolidinyl, 3-methylamino-4-fluoropyrrolidinyl, 3-
25 dimethylamino-4-fluoropyrrolidinyl, 3-aminomethyl-4-fluoro-

pyrrolidinyl, 3-methylaminomethyl-4-fluoropyrrolidinyl, 3-
dimethylaminomethyl-4-fluoropyrrolidinyl, 3-methylamino-4-
chloropyrrolidinyl, 3-aminomethyl-4-chloropyrrolidinyl, 3-
methylaminomethyl-4-chloropyrrolidinyl, 3-(2-hydroxyethyl)-
5 aminomethylpyrrolidinyl, 3-(2-fluoroethyl)aminomethyl-
pyrrolidinyl, 3-amino-4-methylthiopyrrolidinyl, 3-amino-4-
methylsulfinylpyrrolidinyl, 3-formimidoylaminopyrrolidinyl,
3-(2-dimethylhydrazino)pyrrolidinyl, 3-amino-4-methylene-
pyrrolidinyl, piperazinyl, 4-methylpiperazinyl, 3-methyl-
10 piperazinyl, 2-methylpiperazinyl, 3,4-dimethylpiperazinyl,
3,5-dimethylpiperazinyl, 3,3-dimethylpiperazinyl, 3,4,5-
trimethylpiperazinyl, 4-ethoxycarbonylpiperazinyl, 4-t-
butoxycarbonylpiperazinyl, 4-acetylpiperazinyl, 4-benzyloxy-
carbonylpiperazinyl, 4-ethylpiperazinyl, 3,4-diethyl-
15 piperazinyl, 3,4,5-triethylpiperazinyl, 4-ethyl-3,5-
dimethylpiperazinyl, 3-methyl-4-acetylpiperazinyl, 3-methyl-
4-t-butoxycarbonylpiperazinyl, 4-benzylpiperazinyl, 4-n-
propylpiperazinyl, 4-isopropylpiperazinyl, 4-t-butyl-
piperazinyl, 4-cyclopropylpiperazinyl, 4-cyclopentyl-
20 piperazinyl, 4-cyclopropylmethylpiperazinyl, 4-phenyl-
piperazinyl, 4-(p-dimethylaminophenyl)piperazinyl 4-(p-
methoxyphenyl)piperazinyl, 4-(p-fluorophenyl)piperazinyl 3-
phenylpiperazinyl, 3-(p-fluorophenyl)piperazinyl 3-(p-
chlorophenyl)piperazinyl, 3-(p-hydroxyphenyl)piperazinyl 3-
25 (p-methylphenyl)piperazinyl, 4-hydroxyethylpiperazinyl, 4-

aminoethylpiperazinyl, 4-allylpiperazinyl, 4-cinnamyl-
piperazinyl, 4-cyanoethylpiperazinyl, 4-carboxyethyl-
piperazinyl, 4-carboxymethylpiperazinyl, 4-(1,2-dicarboxy-
ethyl)piperazinyl, 4-hydroxypiperazinyl, 4-aminopiperizinyll,
5 3-fluoromethylpiperazinyl, 3-trifluoromethylpiperazinyl, 4-
formimidoylpiperazinyl, 4-acetoimidoylpiperazinyl, 4-
dimethylaminopiperizinyll, 4-hydroxypiperizinyll, morpholino,
2-aminomethylmorpholino, 2-methylaminomorpholino, 2-
dimethylaminomorpholino, thiomorpholino, homopiperazinyl, 4-
10 methylhomopiperazinyl, thiazolizinyll, 3-pyrrolinyll, 3-amino-
methyl-3-pyrrolinyll, oxazolidinyll, imidazolyl and pyrrolyl.

The compounds [I] of the present invention can be con-
verted into both acid addition salts and base addition
salts. Exemplary acid addition salts include (a) the salts
15 with mineral acids such as hydrochloric acid and sulfuric
acid, (b) the salts with organic carboxylic acids such as
formic acid, citric acid, trichloroacetic acid and tri-
fluoroacetic acid, and (c) the salts with sulfonic acids
such as methanesulfonic acid, benzenesulfonic acid, p-
20 toluenesulfonic acid, mesitylenesulfonic acid and
naphthalenesulfonic acid. On the other hand, illustrative
base addition salts include (a) the salts with alkali metals
such as sodium and potassium, (b) the salts with alkaline
earth metals such as calcium and magnesium, (c) the ammonium
25 salt, (d) the salts with nitrogen-containing organic bases

such as trimethylamine, triethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, cyclohexylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-phenamine and N,N'-
5 dibenzylethylenediamine.

The compounds [I] of the present invention may be not only in unsolvated forms but also in hydrated or solvated forms. The present invention therefore embraces the compounds [I] in any crystalline forms and their hydrated and
10 solvated products.

Further, the compounds [I] of the present invention include those containing an asymmetric carbon atom in a substituent group on position 7. They can exist as optically active substances. These optically active substances are
15 also embraced in the compounds of the present invention.

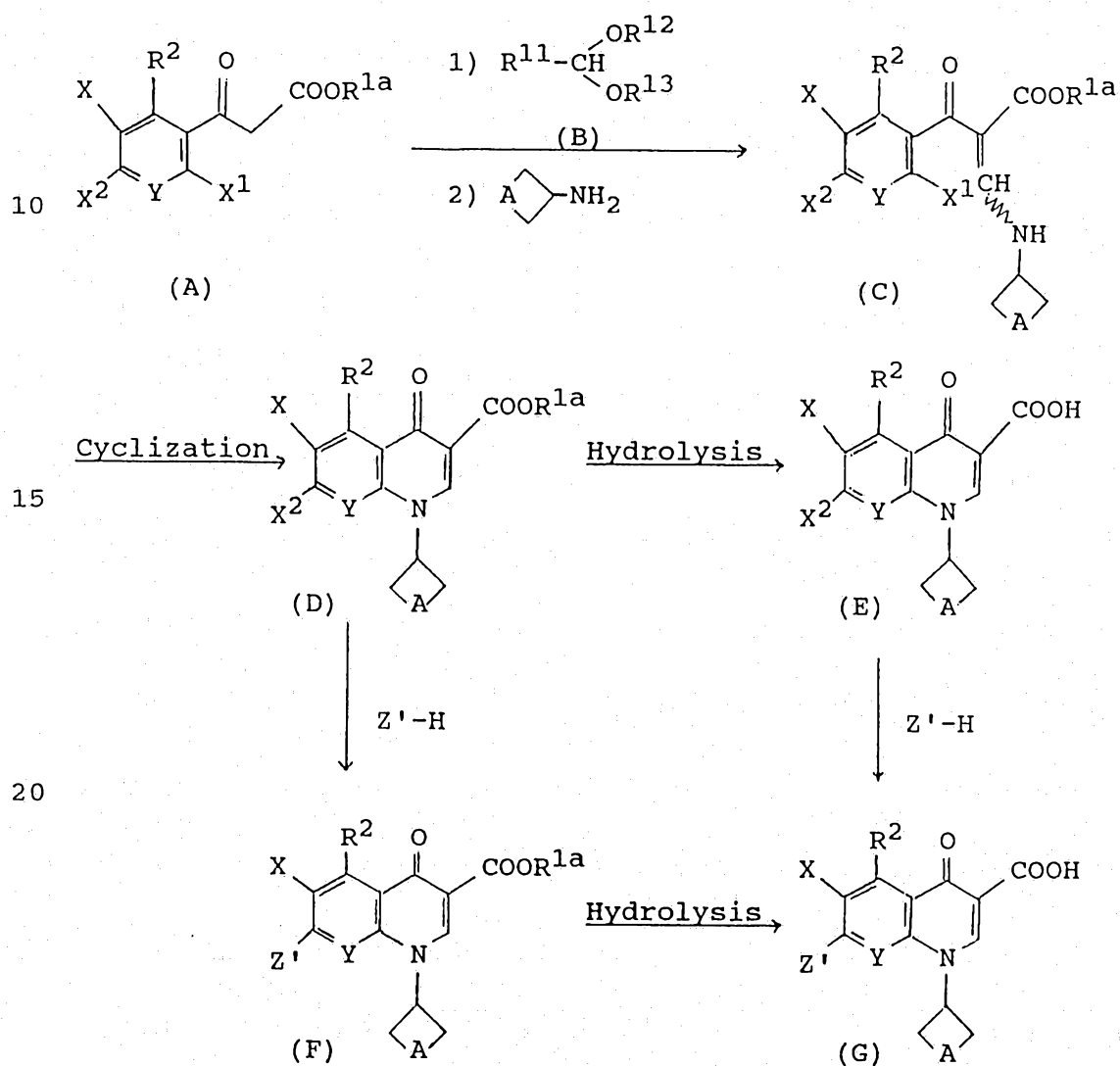
The compounds [I] of the present invention also include those containing two asymmetric carbon atoms in a substituent group on position 7. They can exist as different stereoisomers (cis-form, trans-form). These stereoisomers
20 are also included in the compounds of the present invention.

Each compound [I] of the present invention can be prepared by a process suited for the types of its substituent groups. Preferred preparation processes are as follows:

[Process 1]

The compounds of the formula [I] in which R¹ is a hydrogen atom or a lower alkyl group can be prepared, for example, by the series of steps shown in the following reaction scheme (1):

Reaction Scheme (1)



25 wherein R², X, Y and A have the same meanings as defined

above, X^1 and X^2 individually mean a halogen atom, R^{1a} denotes a lower alkyl group, R^{11} represents a lower alkoxyl group or a group $-N \begin{smallmatrix} R^{14} \\ R^{15} \end{smallmatrix}$ in which R^{14} and R^{15} individually mean a lower alkyl group, R^{12} and R^{13} individually mean a
5 lower alkyl group, and Z' is any one of the groups defined above for Z other than the halogen atoms.

The compound (C) can be obtained by reacting an orthoformic acid ester such as ethyl orthoformate or methyl orthoformate with the compound (A) in acetic anhydride and
10 then reacting the resulting product with the compound $A \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix} NH_2$. The reaction between the compound (A) and the orthoformic acid ester is conducted generally at 0-160°C, preferably at 50-150°C. The reaction time is generally 10 minutes to 48 hours, preferably 1-10 hours. The orthoformic
15 acid ester can be used in at least an equimolar amount, notably in a molar amount 1 to about 10 times relative to the compound (A). The subsequent reaction with the $A \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix} NH_2$ is conducted in a suitable solvent. Any solvent can be used here as long as it does not affect the reaction. Exemplary
20 solvents include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme; aliphatic hydrocarbons such as pentane, hexane, heptane and ligroin; halogenated hydrocarbons such as methylene chloride, chloro-
25 form and carbon tetrachloride; dipolar aprotic solvent such

as dimethylformamide, dimethylsulfoxide; and alcohols such as methanol, ethanol and propanol. The reaction is conducted generally at 0-150°C, preferably 0-100°C. The reaction time generally ranges from 10 minutes to 48 hours. The compound $A-\text{NH}_2$ can be used in at least an equimolar amount, preferably in a molar amount 1-2 times relative to the compound (A).

As an alternative, the compound (C) may be obtained by reaction of compound (a) with an acetal such as N,N-dimethylformamide dimethyl acetal or N,N-dimethylformamide diethyl acetal, followed by the reaction with the compound $A-\text{NH}_2$. Any solvent may be used for the reaction with the acetal as long as it is inert to the reaction. The above-exemplified solvents can be mentioned by way of example.

The reaction is conducted generally at 0-150°C, preferably at room temperature-100°C. The reaction time is generally from 10 minutes to 48 hours, with 1-10 hours being preferred.

The cyclization reaction of the compound (C) is conducted in a suitable solvent in the presence of a basic compound. Any solvent can be used for this reaction as long as it does not affect the reaction. Exemplary solvents include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, tetrahydrofuran, dioxane and monoglyme; halogenated hydrocarbons such as methylene

chloride, chloroform and carbon tetrachloride; alcohols such as methanol, ethanol, propanol and butanol; and dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide. Illustrative usable basic compounds include alkali metals such as metallic sodium and metallic potassium; metal hydrides such as sodium hydride and calcium hydride; inorganic bases such as sodium hydroxide, potassium hydroxide and sodium carbonate; alkoxides such as sodium methoxide, sodium ethoxide and potassium t-butoxide; metal fluorides such as sodium fluoride and potassium fluoride; and organic bases such as triethylamine and 1,8-diazabicyclo[5.4.0]undecene (DBU). The reaction temperature of this reaction is generally 0-200°C, preferably from room temperature to 180°C. The reaction can be brought to completion usually in 5 minutes to 24 hours. The basic compound may be used in an amount of at least an equimolar amount, preferably in a molar amount 1-2 times relative to the compound (C).

The hydrolysis of each of the compounds (D) and (F) can be conducted under the reaction conditions which are employed in usual hydrolysis reactions. For example, the hydrolysis may be carried out in the presence of a basic compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, a mineral acid such as hydrochloric acid, sulfuric acid or hydrobromic acid or an organic acid such as p-toluenesulfonic acid and in a sol-

vent, e.g., water, an alcohol such as methanol, ethanol or propanol, an ether such as tetrahydrofuran or dioxane, a ketone such as acetone or methyl ethyl ketone, or acetic acid, or a mixed solvent thereof. This reaction is conducted generally at room temperature to 180°C, preferably from room temperature to 140°C. The reaction time generally ranges from 1 hour to 24 hours.

The compounds (F) and (G) can be obtained by reacting Z'-H to the compounds (D) and (E), respectively. These reactions are conducted at room temperature to 160°C in a solvent which does not give influence to the reactions, for example, an aromatic hydrocarbon such as benzene, toluene or xylene, an alcohol such as methanol or ethanol, an ether such as tetrahydrofuran, dioxane or monoglyme, a halogenated hydrocarbon such as methylene chloride, chloroform or carbon tetrachloride, a dipolar aprotic solvent such as dimethylformamide, dimethylsulfoxide or N-methylpyrrolidone, acetonitrile, or pyridine, and if necessary, in the presence of an acid-neutralizing agent such as sodium carbonate, calcium carbonate, sodium hydrogencarbonate or triethylamine 1,8-diazabicyclo[5.4.0]undecene (DBU). The reaction time may range from several minutes to 48 hours, preferably from 10 minutes to 24 hours. Z'-H may be used in at least an equimolar amount, preferably in a molar amount 1-5 times relative to the compound (D) or compound (E).

When the starting compounds employed in the above reactions, namely, the starting compounds $A \begin{array}{c} \diagup \diagdown \\ \text{---} \end{array} \text{NH}_2$, $Z'-H$ and/or (A) contain one or more reactive groups which do not take part in the reactions, such as amino, imino, hydroxyl, mercapto and/or carboxyl groups, these starting compounds may be used in a form with these groups being protected, followed by the removal of the protecting groups by a method known *per se* after completion of the reaction. Any protecting groups can be used as long as they can be removed without destroying the structure of the compound of the present invention to be formed by the reaction. Groups usually employed in the chemical field of peptides, aminosaccharides and nucleic acids can be used.

The starting compound (A) can be prepared by any one of the processes described in the following publications or by a similar process.

- 1) J. Heterocyclic Chem. 22, 1033 (1985).
- 2) Liebigs Ann. Chem. 29 (1987).
- 3) J. Med. Chem. 31, 991 (1988).
- 4) J. Org. Chem. 35, 930 (1970).
- 5) Japanese Patent Application Laid-Open (Kokai) No. 246541/1987.
- 6) Japanese Patent Application Laid-Open (Kokai) No. 26272/1987.

7) Japanese Patent Application Laid-Open (Kokai)
No. 145268/1988.

8) J. Med. Chem. 29, 2363 (1986).

9) J. Fluorin Chem. 28, 361 (1985).

5 10) Japanese Patent Application Laid-Open (Kokai)
No. 198664/1988.

11) Japanese Patent Application Laid-Open (Kokai)
No. 264461/1988.

10 12) Japanese Patent Application Laid-Open (Kokai)
No. 104974/1988.

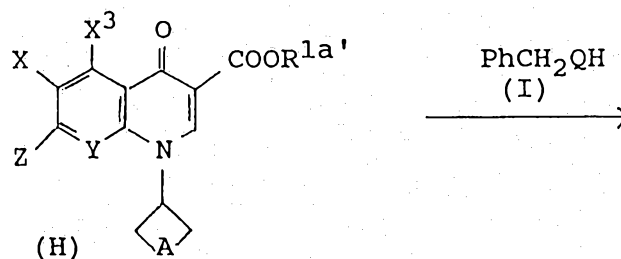
13) Eur. Pat. App. EP 230948.

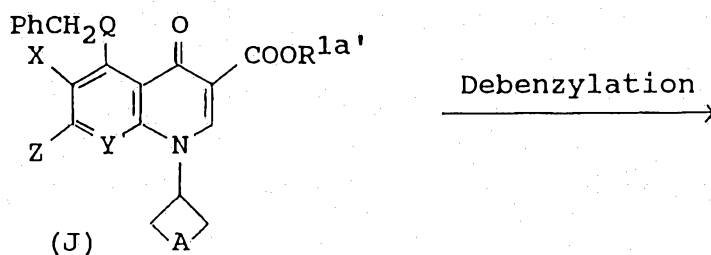
14) Japanese Patent Application Laid-Open (Kokai)
No. 28157/1990.

[Process 2]

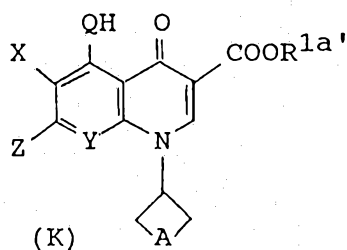
15 Of the compounds represented by the formula [I], those
in which R² is a hydroxyl, amino or mono(lower alkyl)amino
group and, in addition, R¹ is a hydrogen atom or lower alkyl
group can also be prepared by the steps shown in the follow-
ing reaction scheme (2):

20 Reaction Scheme (2)





5



10

wherein R^{1a'}, X and Z have the same meanings, X³ means a halogen atom, preferably F, and Q represents -O-, -NH- or -NR¹⁶- in which R¹⁶ is a lower alkyl group.

15

The compound (J) can be obtained by reacting the compound represented by the formula (H) with the compound (I), and if necessary, in the presence of an acid-neutralizing agent. Solvents which are usable in this reaction are those giving no influence to the reaction, including aromatic hydrocarbons such as toluene and xylene, ethers such as tetrahydrofuran, dioxane and monoglyme, halogenated hydrocarbons such as methylene chloride and chloroform, dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide, acetonitrile and pyridine. The reaction temperature may be usually 0-150°C, preferably from room temperature to about 120°C. The reaction can generally be brought to completion approximately in 10 minutes to 24

25

hours.

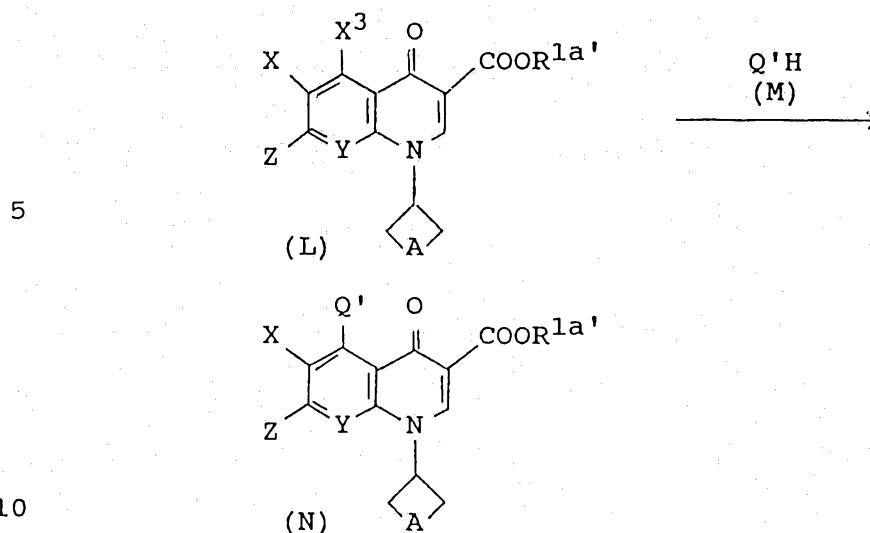
The compound (I) may be used in at least an equimolar amount, preferably in a molar amount 1-1.5 times relative to the compound (H). As the acid-neutralizing agent, it is possible to employ the same acid-neutralizing agent as that usable in the reaction of the compound (D) or compound (E) with Z'-H.

For the debenzylation of the compound (J), the reaction conditions employed in any usual catalytic reduction can be applied. It can be conducted, for example, by stirring the compound (J) in the presence of a catalyst such as palladium/carbon, palladium black or platinum dioxide, in a solvent such as methanol, ethanol, propanol, acetic acid, tetrahydrofuran, dioxane, ethyl acetate or water or in a mixed solvent thereof, generally under the atmosphere of hydrogen gas at a pressure of 1-100 atm. The reaction temperature generally ranges from room temperature to 100°C. The reaction is generally brought to completion in 1-48 hours.

[Process 3]

Among the compounds represented by the formula [I], those having a hydrogen atom or a lower alkyl group as R¹ and a hydroxyl, lower alkoxy, amino, or mono- or di-lower alkyl group as R² can also be prepared by the reaction step shown in the following reaction scheme (3):

Reaction Scheme (3)



wherein $R^{1a'}$, A, X, X^3 , Y and Z have the same meanings as defined above, and Q' represents a hydroxyl, lower alkoxyl, amino, or mono- or di(lower alkyl)amino group.

15 The compound (N) can be obtained by reacting the compound (L) with the compound (M), and if necessary, in the presence of an acid-neutralizing agent. Any solvent may be used here as long as it does not affect the reaction. For example, the solvents usable in the reaction between the compound (H) and the compound (I) and their mixed solvents

20 can be used. The reaction temperature may generally range from 0°C to 150°C , with room temperature to about 120°C being preferred. The reaction can be brought to completion generally in 10 minutes to 24 hours. The compound represented by the formula (M) may be used in an amount ranging from an

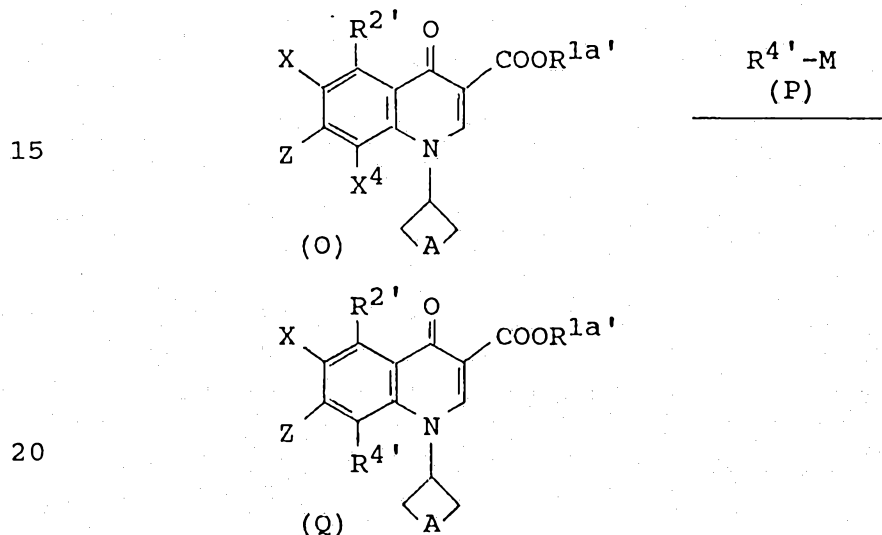
25 equimolar amount to a large excess amount, relative to the

compound (L). When the compound (L) is volatile, the reaction may be conducted in a closed system, for example, by using an autoclave or the like. As the acid-neutralizing agent, those exemplified above can be used.

5 [Process 4]

Of the compounds [I], those represented by the formula [I] in which R^1 is a hydrogen atom or a lower alkyl group, Y is $C-R^4'$, R^4' being a lower alkoxy group, and R^2' is one of the groups defined above other than the halogen atoms can also be prepared by the reaction step shown in the following reaction scheme (4):

Reaction Scheme (4)



wherein $R^{1a'}$, A, X and Z have the same meanings as defined above, R^2' means one of the groups defined above for R^2 other than the halogen groups, X^4 represents a halogen atom, preferably F or Cl, R^4' denotes a lower alkoxy group, and M

25

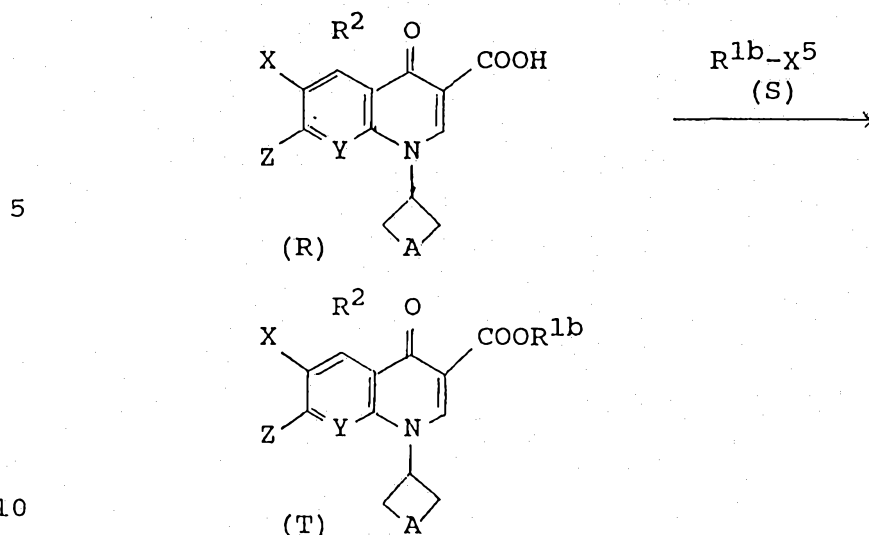
is an alkali metal atom.

The compound (Q) can be obtained by reacting the compound (O) with the compound (P). Exemplary preferred solvents usable in this reaction include solvents inert to the reaction and mixed solvents thereof, for example, alcohols corresponding to $R^{4'}$ and in addition, aromatic hydrocarbons such as benzene and toluene, ethers such as tetrahydrofuran and dioxane, dipolar aprotic solvents such as dimethylformamide, dimethylsulfoxide, HMPA and N-methylpyrrolidone, acetonitrile, pyridine and the like. The reaction temperature generally ranges from room temperature to 150°C, preferably from room temperature to about 100°C. The reaction can be brought to completion generally in 10 minutes to 24 hours. The compound (P) can be used in an equimolar amount to a large excess amount, preferably an equimolar amount to a five fold molar amount, relative to the compound (O).

[Process 5]

Among the compounds represented by the formula [I], those containing a carboxyl-protecting group as R^1 can be prepared, for example, by the reaction step shown in the following reaction scheme (5):

Reaction Scheme (5)



wherein R^2 , A, X, Y and Z have the same meanings as defined above, R^{1b} means a carboxyl-protecting group, and X^5 denotes a halogen atom.

15 The compound (T) can be obtained by reacting the compound (R) with the compound (S). Exemplary solvents usable in the reaction include inert solvents, for example, aromatic hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as methylene chloride and chloroform, dipolar aprotic solvents such as dimethyl-
 20 formamide and dimethylsulfoxide, and acetonitrile. The reaction temperature generally ranges from room temperature to about 100°C. Preferably, this reaction is carried out in the presence of a basic compounds such as triethylamine, diisopropylethylamine, dicyclohexylamine, DBU, sodium car-
 25 bonate, potassium carbonate or sodium hydroxide.

Among the compounds represented by the formula [I], those containing a primary or secondary amino group as the heterocyclic group indicated by Z can be converted to the compounds which have a formimidoyl or lower alkylimidoyl group on the amino group by reacting with formimidic acid ester or lower alkanecarboximidic acid ester.

The thus-obtained compounds of the present invention can be isolated and purified by methods known *per se* in the art. They are obtained in the form of salts, free carboxylic acids or free amines, depending on the conditions for isolation and purification. However, they can be converted mutually from one of these forms into another one, whereby the compounds of the present invention can be prepared in a desired form.

[Action]

(1) Antibacterial activities:

With respect to certain representative compounds among the compounds [I] of the present invention, their minimum inhibitory concentrations (MIC; $\mu\text{g/ml}$) were measured in accordance with the standard method established by the Japan Society of Chemotherapy [CHEMOTHERAPY, 29(1), 76-79 (1981)]. The results are summarized in Table 1, in which the compound numbers are as shown in examples.

Table 1

	Compound No.	Minimum inhibitory concentration (μg/ml)		
		<i>E. coli</i> NIH JC-2 (IFO 12734)	<i>S. aureus</i> 209 P (IFO 12732)	<i>P. aeruginosa</i> (IFO 3445)*
5	4	0.39	0.2	1.56
	5	0.39	0.39	6.25
	6	0.78	0.78	6.25
	7	0.78	0.39	3.13
	9	0.39	0.2	3.13
10	11	0.2	1.56	1.56
	12	0.2	1.56	1.56
	13	0.2	1.56	1.56
	14	0.2	3.13	3.13
	15	0.78	0.39	6.25
15	16	0.39	0.78	1.56
	17	0.78	3.13	6.25
	18	0.39	1.56	1.56
	19	0.2	1.56	3.13
	20	1.56	0.2	3.13
20	21	0.39	0.39	3.13
	22	6.25	0.78	>25
	27	0.39	0.2	3.13
	28	0.78	0.78	6.25
	29	0.1	0.78	0.78

Table 1 (Cont'd)

Compound No.	Minimum inhibitory concentration ($\mu\text{g/ml}$)		
	<i>E. coli</i> NIH JC-2 (IFO 12734)	<i>S. aureus</i> 209 P (IFO 12732)	<i>P. aeruginosa</i> (IFO 3445)*
30	0.78	0.2	3.13
31	0.2	0.39	0.78
32	0.78	0.1	3.13
35	0.2	1.56	3.13
36	0.39	3.13	3.13
37	0.39	1.56	1.56
38	3.13	0.39	12.5
39	0.39	1.56	6.25
40	0.39	0.78	6.25
41	0.78	12.5	6.25
42	0.78	1.56	3.13
44	0.39	1.56	1.56
45	0.39	1.56	3.13
46	0.78	0.1	3.13
47	0.78	0.2	6.25
48	0.39	1.56	3.13
49	0.78	1.56	3.13
50	0.39	0.78	1.56
51	0.78	1.56	3.13
52	0.78	0.1	3.13
53	0.2	0.1	3.13

Table 1 (Cont'd)

Compound No.	Minimum inhibitory concentration ($\mu\text{g/ml}$)		
	<i>E. coli</i> NIH JC-2 (IFO 12734)	<i>S. aureus</i> 209 P (IFO 12732)	<i>P. aeruginosa</i> (IFO 3445) *
55	0.39	0.78	0.78
58	0.78	0.39	6.25
59	0.39	0.39	3.13
61	0.39	3.13	1.56
65	0.2	1.56	0.39
66	0.39	3.13	3.13
68	0.39	3.13	0.78
69	0.39	3.13	1.56
70	1.56	0.39	6.25
72	0.39	0.2	3.13
73	0.78	0.78	6.25
76	0.39	0.2	1.56
77	1.56	1.56	12.5
79	1.56	0.1	25
81	0.78	0.78	3.13
82	1.56	0.78	12.5
85	1.56	3.13	6.25
86	0.39	1.56	3.13
88	0.78	6.25	3.13
89	0.78	1.56	3.13
90	0.2	0.2	1.56

Table 1 (Cont'd)

Compound No.	Minimum inhibitory concentration ($\mu\text{g/ml}$)		
	<i>E. coli</i> NIH JC-2 (IFO 12734)	<i>S. aureus</i> 209 P (IFO 12732)	<i>P. aeruginosa</i> (IFO 3445) *
91	0.2	0.78	1.56
92	0.1	0.39	1.56
93	0.78	1.56	3.13
94	0.2	0.78	1.56
95	0.2	1.56	3.13
96	0.1	0.39	0.78
97	0.39	0.78	1.56
101	0.1	0.2	0.78
102	0.1	0.39	0.78
103	0.1	0.2	0.39
107	0.78	3.13	6.25
108	0.78	0.78	3.13
109	0.39	0.78	3.13
110	0.78	1.56	6.25

* IFO: Institute for Fermentation Osaka

(2) Partition coefficient:

Following the method proposed by Akira Tsuji et al. in Antimicrob. Agents Chemother., 32, 190-194 (1988), 50 mM phosphate buffer (pH 7.4, $\mu=0.15$)/n-octanol partition coefficients were measured. The measurement results of representative compounds are shown in Table 2.

Table 2

Compound No.	Partition coefficient
29	0.465 $\pm$ 0.001
113	0.296 $\pm$ 0.003

5

(3) Interaction with fenbufen and toxicological study:

These activities were studied by the coadministration test with fenbufen, according to the method of Yamamoto et, al. (Chemotherapy, 36, 300-324, 1988).

10 Preparation of materials

Fenbufen and the quinolone compounds were each diluted with a solution of 0.5% methylcellulose.

Test method

15 A dose of 200 mg/kg of fenbufen was administered by oral route to groups of 10 mice (female, ICR, 18-23 g) 90 minutes before administration of the quinolone compounds by oral route, at a dose of 500 mg/kg. The number of animals i each group who showed a convulsion activity during two hours following the administration of the compound of this inven-
20 tion was noted. Following the 24 hours number of survival animals was noted. The results are recorded in the following table.

Table 3

	Quinolone compound + fenbufen	Induction of convulsion number of positive mice	Mortality number of dead mice
5	Compound 29	0/10	0/10
	Compound 117	0/10	0/10
	Enoxacin	10/10	10/10

The compounds of this invention benefit from good tolerance to a convulsion caused by drug interactions with antiinflammatory drug and show weak toxicity.

As has been described above, the compounds [I] and their salts according to the present invention are all novel compounds, exhibit extremely high antibacterial activities against gram-negative bacteria and gram-positive bacteria, and have high safety.

When the compounds [I] and their salts according to the present invention are used as antibacterial agents, they can be formulated into preparations along with a pharmaceutically-acceptable carrier for parenteral administration such as injection or rectal administration or for oral administration in the form of a solid or a liquid.

Preparations of this invention for use as injections can take the form of solutions, suspensions or emulsions in pharmaceutically-acceptable germ-free water or non-aqueous liquid. Exemplary suitable non-aqueous carriers, diluents,

solvents and vehicles include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These preparations can contain one or more auxiliary agents, for example, antiseptics, wetting agents, emulsifiers and dispersants. These formulations can be sterilized, for example, by filtering them through a bacterial filter or by mixing, immediately before use, a sterilizing agent in the form of a germ-free solid composition soluble in sterilized water or one of some other media which can be sterilized and injected.

Exemplary solid preparations for oral administration include capsules, tablets, pills, powders, granules, etc. Upon formulation of these solid preparations, the compounds and their salts according to the present invention are generally mixed with at least one inert extender such as sucrose, lactose or starch. One or more materials other than inert extenders, for example, a lubricant such as magnesium stearate can also be incorporated in the preparations upon formulation of the latter in a usual manner. A buffer can also be incorporated in the case of capsules, tablets and pills. Tablets and pills can be applied with an enteric coating.

Illustrative liquid preparations includes pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs, which contain an inert diluent employed common-

ly by those skilled in the art, for example, water. In addition to such an inert diluent, the liquid preparations can also be added with one or more auxiliary agents, for example, wetting agents, emulsifiers, suspending agents,
5 sweetening agents, seasoning agents and perfumes.

Preparations for rectal administration are preferably suppositories which may contain an excipient such as cacao butter or suppository wax in addition to a compound or its salt according to the present invention.

10 The dosage of the compounds [I] and their salts according to the present invention generally ranges from about 0.1 mg/kg to 1,000 mg/kg per day, with about 1-100 mg/kg per day being preferred especially. If desired, this daily dosage can be administered in 2-4 portions.

15 The present invention will hereinafter be described by the following examples.

Example 1

Ethyl 3-(oxetan-3-yl-amino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (Compound No. 1)

20 3,3 g of ethyl 2,3,4,5-tetrafluorobenzoylacetate, 3.1 ml of ethyl orthoformate and 5.3 ml of acetic anhydride were reacted at 130°C for 4 hours. After volatile components were distilled off under reduced pressure, the residue was dissolved in 60 ml of benzene, followed by the
25 addition of 1 g of 3-aminooxetane at room temperature.

After they were reacted at the same temperature for 18 hours, the solvent was distilled off. The residue was subjected to column chromatography on silica gel (chloroform/ethyl acetate = 4/1), whereby 3.54 g of the title compound 5 was obtained as an oil-like yellow substance.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.11(t, $J=7\text{Hz}$, 3H), 4.08(q, $J=7\text{Hz}$, 2H), 4.7-4.8(m, 3H),
4.9-5.05(m, 2H), 6.95-7.05(m, 1H), 8.09(d, $J=13.6\text{Hz}$, 1H).

Example 2

10 Ethyl-1-(oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 2)

1.57 g of Compound No. 1 was dissolved in 15 ml of dimethylformamide, followed by the addition of 650 mg of potassium carbonate. The resultant mixture was reacted at 15 160°C for 10 minutes. After the solvent was distilled off, the residue was extracted with 50 ml of chloroform. The organic layer was washed with water and then dried over MgSO_4 . The solvent was thereafter distilled off. The residue was crystallized from hexane-chloroform, whereby 1 g 20 of the title compound was obtained as slightly yellow needle crystals.

Melting point: 146-147°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.4 (t, $J=7\text{Hz}$, 3H), 4.4 (q, $J=7\text{Hz}$, 2H), 4.95-5.2 (m, 4H),
5.7-5.9 (m, 1H), 8.1-8.2 (m, 1H), 8.68 (s, 1H).

Example 3

5 1-(Oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-
oxoquinoline-3-carboxylic acid (Compound No. 3)

1 g of Compound No. 2 was reacted under reflux for 1
hour in the mixture of 20 ml of ethanol, 4 ml of
tetrahydrofuran and 24 ml of a 10% solution of sodium car-
10 bonate. After the organic solvents were distilled off, the
residue was acidified with 1N-HCl and then extracted with
chloroform. The organic layer was washed with water and
then dried over MgSO_4 , and the organic solvent was distilled
off. The residue was crystallized from chloroform-hexane,
15 whereby 790 mg of the title compound was obtained as slight-
ly yellow needle crystals.

Melting point: 203-206°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

4.98-5.26 (m, 4H), 5.8-6.0 (m, 1H), 8.2-8.3 (m, 1H),
20 8.92 (s, 1H).

Example 4

6,8-Difluoro-1-(oxetan-3-yl)-7-(pyrrolidin-1-yl)-1,4-
dihydro-4-oxoquinoline-3-carboxylic acid
(Compound No. 4)

25 100 mg of Compound No. 3 and 71 mg of pyrrolidine were

reacted at 80°C for 1 hour in 1 ml of DMF. After the solvent was distilled off, the residue was extracted with chloroform. The organic layer was washed with 5% acetic acid and water, and then dried over MgSO_4 . The solvent was
5 distilled off and the residue was crystallized from chloroform-ethanol, whereby 37 mg of the title compound was obtained as colorless needle crystals.

Melting point: 261-262°C.

^1H -NMR (CDCl_3 + DMSO-d_6) δ :

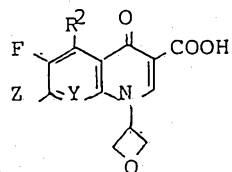
10 1.85-2.0(m,4H), 3.6-3.7(m,4H), 4.85-5.1(m,4H),
5.8-5.9(m,1H), 7.74(d,J=14Hz,1H), 8.66(s,1H).

Example 5

Compound Nos. 5-9 and Compound Nos. 11-22, which are
shown in Table 4, were obtained in a similar manner to Exam-
15 ple 4.

20

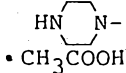
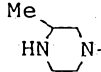
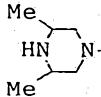
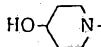
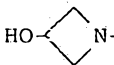
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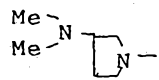
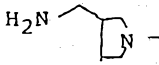
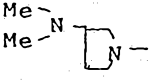
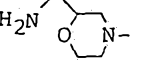
[Table 4-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
5	H		CF	Yellow solid	254-250	[DMSO-d ₆]: 4.5-4.6(m,4H), 4.9-5.1(m,4H), 5.8-5.9(m,1H), 5.98(s,2H), 7.76(dd,J=14Hz,J=2Hz,1H), 8.64(s,1H)	DMF
6	H		CF	Colorless plate crystals	266.3	[CDCl ₃]: 3.3-3.4(m,4H), 3.8-3.9(m,4H), 5.0-5.2(m,4H), 5.8-5.9(m,1H), 7.97(dd,J=11Hz,J=1.5Hz), 8.77(s,1H)	DMF
7	H		CF	Yellowish white solid	277.2	[CDCl ₃]: 2.7-2.8(m,4H), 3.4-3.5(m,4H), 4.9-5.2(m,4H), 5.8-5.9(m,1H), 7.98(dd,J=11.4Hz,J=1.5Hz,1H), 8.79(s,1H)	DMF
8	H		CF	Colorless solid	180.5-181.5	[CDCl ₃]: 5.0-5.2(m,4H), 5.8-6.0(m,1H), 7.26(s,1H), 7.33(s,1H), 7.81(s,1H), 8.31(dd,J=10Hz,2Hz,1H), 8.90(s,1H)	DMF
9	H		CF	Red solid	248.5-250.5	[DMSO-d ₆]: 4.9-5.3(m,8H), 5.8-6.0(m,1H), 7.2-7.5(m,4H), 7.85(d,J=10Hz,1H), 8.7(s,1H)	DMF
11	H	Me-N	CF	Yellow plate crystals	221.9	[CDCl ₃]: 2.37(s,3H), 2.5-2.6(m,4H), 3.3-3.5(m,4H), 4.92-5.2(m,4H), 5.8-5.9(m,1H), 7.94(dd,J=12Hz,2Hz,1H), 8.76(s,1H)	DMF

[Table 4-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
12	H		CF	White solid	252-254	[DMSO-d ₆]: 1.9(s,3H), 2.75-2.9(m,4H), 3.2-3.35(m,4H), 4.9-5.15(m,4H), 5.85-5.95(m,1H), 7.84(d,J=11Hz,1H), 8.77(s,1H)	DMSO+DBU
13	H		CF	Yellow solid	228.5-229	[DMSO-d ₆]: 0.97(d,J=5Hz,3H), 2.6-2.9(m,3H), 3.0-3.4(m,4H), 5.8-6.0(m,1H), 4.9-5.1(m,4H), 7.83(d,J=12Hz,1H), 8.74(s,1H)	DMSO
14	H		CF	Yellow solid	239.5-240	[DMSO-d ₆]: 0.97(d,J=6.2Hz,6H), 2.8-2.9(m,2H), 3.0-3.4(m,4H), 4.9-5.1(m,4H), 5.8-6.0(m,1H), 7.82(dd,J=12Hz,1.5Hz,1H), 8.76(s,1H)	DMSO
15	H		CF	Yellow needle crystals	263.5-264	[CDCl ₃ +DMSO-d ₆]: 1.6-1.8, 1.9-2.05(m,4H), 3.15-3.3, 3.45-3.6(m,4H), 3.8-3.9(m,1H), 4.95-5.2(m,4H), 5.82-5.95(m,1H), 7.9(dd,J=12Hz,2Hz,1H), 8.79(s,1H)	DMF
16	H		CF	Yellow powder	254-256	[DMSO-d ₆]: 1.75-2.0(m,2H), 3.2-4.0(m,4H), 4.3-4.4(brs,1H), 4.85-5.15(m,4H), 5.75-5.9(m,1H), 7.73(d,J=13.9Hz,1H), 8.62(s,1H)	DMF+DBU
17	H		CF	Yellow solid	253-254.5	[DMSO-d ₆]: 4.05-4.2(brs,2H), 4.5-4.7(brs,3H), 4.95-5.15(m,4H), 5.75-5.9(m,1H), 7.71(d,J=12.5Hz,1H), 8.67(s,1H)	DMF+DBU

[Table 4-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
18	H		CF	Brown powder	160-163	[DMSO-d ₆]: 1.8-2.0(m,2H), 3.3-4.0(m,5H), 4.85-5.1(m,4H), 5.75-5.95(m,1H), 7.76(d,J=12Hz,1H), 8.65(s,1H)	DMSO+DBU
19	H		CF	Yellow powder	241-242	[DMSO-d ₆ +D ₂ O]: 2.05-2.5(m,2H), 2.87(s,6H), 3.75-4.05(m,4H), 4.1-4.3(m,1H), 4.9-5.2(m,4H), 5.85-5.95(m,1H), 7.73(d,J=13.2Hz,1H), 8.69(s,1H)	DMF+DBU
20	H		CF	Yellow powder	152-154	[DMSO-d ₆]: 1.5-2.1(m,2H), 2.6-3.0(m,2H), 3.0-3.6(m,5H), 4.83-5.07(m,4H), 5.72-5.95(m,1H), 7.72(d,J=12Hz,1H), 8.63(s,1H)	DMSO+DBU
21	H		CF	Yellow solid	228.5-229	[DMSO-d ₆ +MeOH-d ₄]: 1.65-1.85, 2.1-2.2(m,2H), 2.5-2.8(m,2H), 2.86(s,6H), 3.45-3.95(m,5H), 4.9-5.15(m,4H), 5.8-5.95(m,1H), 7.75(d,J=12Hz,1H), 8.66(s,1H)	DMF+DBU
22	H		CF	White solid	194-194.5	[DMSO-d ₆]: 2.9-3.1(m,2H), 3.2-3.5(m,4H), 3.5-4.1(m,3H), 4.85-5.15(m,4H), 5.8-6.0(m,1H), 7.89(d,J=11.7Hz,1H), 8.76(s,1H)	DMF+DBU

Example 6

6,8-Difluoro-7-ethoxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 10)

In Example 3, the mother liquor from which Compound No. 3 had been crystallized was concentrated. Hexane was added to the concentrate to solidify the same, whereby the title compound was obtained as a colorless solid.

Melting point: 175-176°C.

¹H-NMR (CDCl₃) δ:

1.46(t, J=7Hz, 3H), 4.41(q, J=7Hz, 2H), 5.0-5.2(m, 4H),
5.8-5.95(m, 1H), 8.07(d, J=11Hz, 1H), 8.83(s, 1H).

Example 7

Ethyl 1-(oxetan-3-yl)-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 23)

14.1 g of ethyl 2,3,4,5,6-pentafluorobenzoylacetate,
12.5 ml of ethyl orthoformate and 21.2 ml of acetic anhydride were reacted at 130°C for 3 hours. The solvent was distilled off under reduced pressure and 100 ml of benzene were added to the oily residue. At room temperature, 4.02 g of 3-aminooxetane were added, followed by stirring at the same temperature for 1 day. Benzene was distilled off, and upon addition of hexane, a yellow solid was formed. The solid was collected by filtration and then reacted at 140°C for 10 minutes in the mixture of 4.73 g of potassium carbonate and 50 ml of dimethylformamide. The solvent was

distilled off, followed by extraction with 200 ml of chloroform. After the organic layer was washed with water and dried over MgSO_4 , the solvent was distilled off. The residue was subjected to column chromatography on silica gel (chloroform/ethyl acetate = 2/1), whereby the title compound was obtained as a yellow oily substance. Upon addition of hexane, the substance was solidified so that 7.94 g of the title compound was obtained as a yellow solid.

Melting point: 110-113°C.

10 ^1H -NMR (CDCl_3) δ :

1.4 (t, $J=7\text{Hz}$, 3H), 4.39 (q, $J=7\text{Hz}$, 2H), 4.9-5.2 (m, 4H),
5.7-5.8 (m, 1H), 8.55 (s, 1H).

Example 8

15 Ethyl 5-benzylamino-1-(oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 24)

3 g of Compound No. 23, 931 mg of benzylamine and 2.35 g potassium carbonate were reacted under reflux for 1 hour in 20 ml of acetonitrile. The solvent was distilled off, followed by extraction with 100 ml of chloroform.

20 After the organic layer was washed with water and dried over MgSO_4 , the solvent was distilled off. The residue was subjected to column chromatography on silica gel (chloroform/ethyl acetate = 10/1), whereby 2 g of the title compound was obtained as a yellow solid.

25 Melting point: 127-128.5°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.39 (t, $J=7\text{Hz}$, 3H), 4.39 (q, $J=7\text{Hz}$, 2H), 4.6-4.75 (m, 2H),
4.85-5.15 (m, 4H), 5.6-5.7 (m, 1H), 7.2-7.5 (m, 5H),
8.43 (s, 1H).

5 Example 9

Ethyl 5-amino-1-(oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 25)

1.2 g of Compound No. 24 was dissolved in the liquid mixture of 17 ml of tetrahydrofuran, 30 ml of ethanol and 10 ml of acetic acid, to which 500 mg of 10% Pd/C was added. They were reacted under normal pressure and hydrogen gas at room temperature for 16 hours. The reaction mixture was filtered through a Celite (trade mark) pad and the filtrate was concentrated. Ethanol was added to the residue. 15 The resulting solid was collected by filtration, whereby 830 mg of the title compound was obtained as a colorless solid.

Melting point: 111-112°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

20 1.4 (t, $J=7\text{Hz}$, 3H), 4.4 (q, $J=7\text{Hz}$, 2H), 4.9-5.2 (m, 4H),
5.6-5.8 (m, 1H), 6.8-7.2 (br, 2H), 8.47 (s, 1H).

Example 10

5-Amino-1-(oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 26)

25 600 mg of Compound No. 25 was reacted under reflux for

30 minutes in a mixture of 20 ml of ethanol, 20 ml of tetrahydrofuran and 15 ml of 10% sodium carbonate solution. After the organic solvents were distilled off, the pH of the residue was adjusted to 7-6 with acetic acid. The resultant mixture was subjected to centrifugation at 3,000 rpm for 10 minutes and the supernatant was removed by decantation. Using 10 ml of water, 10 ml of ethanol and 10 ml of ether successively, centrifugation and decantation were repeated so that the precipitate was washed. After ether was removed by decantation, the residue was dried under reduced pressure whereby 280 mg of the title compound was obtained as a yellow solid.

Melting point: 197-198°C.

$^1\text{H-NMR}$ (DMSO- d_6) δ :

4.8-5.2(m, 4H), 5.6-5.8(m, 1H), 7.7-8.0(br, 2H), 8.65(s, 1H).

Example 11

5-Amino-6,8-difluoro-1-(oxetan-3-yl)-7-(pyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

(Compound No. 27)

60 mg of Compound 26 and 43 mg of pyrrolidine were reacted at 80°C for 1 hour in 1 ml of dimethylformamide. After the solvent was distilled off, the residue was solidified with 10 ml of ethanol. The solid was collected by filtration. The solid was washed with ethanol and ether,

whereby 13 mg of the title compound was obtained as a yellow solid.

Melting point: 250-253°C.

$^1\text{H-NMR}$ (DMSO-d_6) δ :

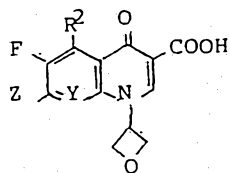
5 1.65-2.0(brs,4H), 3.4-3.8(brs,4H), 4.7-5.0(m,4H),
 5.6-5.8(m,1H), 7.0-7.3(br,2H), 8.45(s,1H).

Example 12

Compound Nos. 28-32 and Compound Nos. 148-181, which are shown in Table 5, were obtained in a similar manner to
10 Example 11.

In the subsequent examples, Isomers A and B will indicate those obtained by using starting compounds (raw materials employed to form Z in the formula [I]) isolated by the following procedure.

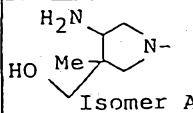
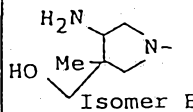
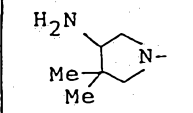
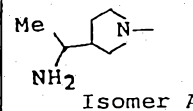
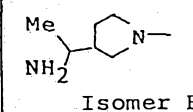
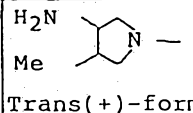
15 Compounds obtained using raw materials eluted first by column chromatography on silica gel (eluent: $\text{CHCl}_3/\text{CH}_3\text{OH}$) or raw materials easily crystallized out of ether solution will be designated as Isomers A, while compounds obtained using raw materials eluted later by the chromatography on the
20 silica gel column or raw materials not crystallized easily with ether will be designated as Isomers B.



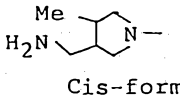
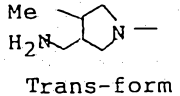
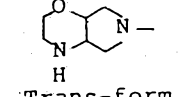
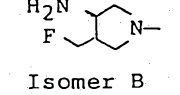
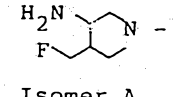
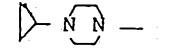
[Table 5-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
28	-NH ₂		CF	Yellow solid	223-225	[CDCl ₃ + DMSO-d ₆]: 2.6-2.8(bris,4H), 3.4-3.6(bris,4H), 4.85-5.2(m,4H), 5.6-5.8(m,1H), 6.5-6.7(bris,2H), 8.59(s,1H)	DMF
29	-NH ₂		CF	Yellow solid	235-237	[CDCl ₃ + DMSO-d ₆]: 2.35(s,3H), 2.5-2.7(bris,4H), 3.3-3.45(bris,4H), 4.8-5.1(m,4H), 5.6-5.8(m,1H), 6.6-6.8(bris,2H), 8.57(s,1H)	DMF
30	-NH ₂		CF	Yellow solid	264-265	[DMSO-d ₆ + CDCl ₃]: 4.8-5.2(m,4H), 3.27(bris,4H), 5.7-5.8(m,1H), 7.0-7.2(br,2H), 7.2-7.4(m,4H), 8.53(s,1H)	DMF
31	-NH ₂		CF	Yellow solid	200-203	[DMSO-d ₆]: 1.9-2.1(m,2H), 3.3-4.1(m,5H), 4.8-5.1(m,4H), 5.6-5.8(m,1H), 7.3-7.5(br,2H), 8.46(s,1H)	DMF+Et ₃ N
32	-NH ₂		CF	Yellow solid	128-130	[DMSO-d ₆]: 1.5-2.2(m,2H), 2.7-3.0(m,2H), 3.0-3.8(m,5H), 4.7-5.0(m,4H), 5.6-5.8(m,1H), 7.1-7.3(br,2H), 8.44(s,1H)	DMF + Et ₃ N
148	NH ₂		CF	Pale Yellow powder	261-263	[DMSO-d ₆]: 1.24(s,3H), 1.73(bris,2H), 3.75-3.9(m,1H), 4.75-5.0(m,4H), 5.6-5.8(m,1H), 7.18(bris,2H), 8.43(s,1H)	DMSO + Et ₃ N

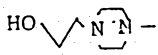
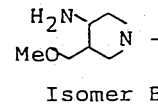
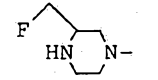
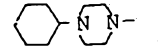
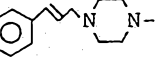
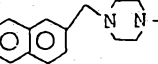
[Table 5-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
149	NH ₂	 Isomer A	CF	Pale Yellow powder	271-276	[DMSO-d ₆]: 1.03(s,3H), 3.5-4.1(m,4H), 4.8-5.1(m,4H), 5.55-5.8(m,1H), 7.16(brs,2H), 8.45(s,1H)	DMSO + Et ₃ N
150	NH ₂	 Isomer B	CF	Pale Yellow powder	≥300 (decomposed)	[DMSO-d ₆]: 0.91(s,3H), 3.6-3.8(m,2H), 4.7-5.1(m,4H), 5.6-5.8(m,1H), 7.15(brs,2H), 8.45(s,1H)	DMSO + Et ₃ N
151	NH ₂		CF	Pale Yellow powder	≥210 (colored & decomposed)	[DMSO-d ₆]: 1.06(s,3H), 1.13(s,3H), 3.58-3.75(m,2H), 3.9-4.05(m,1H), 4.75-5.05(m,4H), 5.6-5.8(m,1H), 7.23(brs,2H), 8.46(s,1H)	DMSO + Et ₃ N
152	NH ₂	 Isomer A	CF	Yellow powder	209-213	[DMSO-d ₆]: 1.17(d,J=6.43Hz,3H), 1.55-1.8(m,1H), 2.0-2.3(m,2H), 4.7-5.0(m,4H), 5.6-5.8(m,1H), 7.20(brs,2H), 8.44(s,1H)	DMSO + Et ₃ N
153	NH ₂	 Isomer B	CF	Yellow powder	≥251 (colored & decomposed)	[DMSO-d ₆]: 1.25(s,3H), 1.55-1.8(m,1H), 1.95-2.1(m,1H), 2.2-2.4(m,1H), 4.75-5.05(m,4H), 5.6-5.8(m,1H), 7.19(brs,2H), 8.41(s,1H)	DMSO + Et ₃ N
154	NH ₂	 Trans(+)-form	CF	Yellow powder	≥240 (decomposed)	[DMSO-d ₆]: 1.07(d,J=5.86Hz,3H), 2.20-2.4(m,1H), 3.5-3.8(m,2H), 3.9-4.1(m,1H), 4.75-5.05(m,4H), 5.6-5.8(m,1H), 7.25(brs,2H), 8.45(s,1H)	DMSO + Et ₃ N

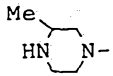
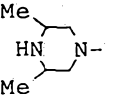
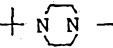
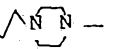
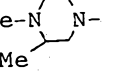
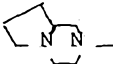
[Table 5-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
155	NH ₂	 Cis-form	CF	Pale yellow powder	176-183	[DMSO-d ₆]: 0.97(d, J=6.4Hz, 3H), 2.42(brs, 2H), 2.7-3.0(m, 2H), 3.5-3.9(m, 3H), 4.75-5.02(m, 4H), 5.6-5.75(m, 1H), 7.17(brs, 2H), 8.43(s, 1H)	DMSO + Et ₃ N
156	NH ₂	 Trans-form	CF	Pale yellow powder	171-178	[DMSO-d ₆]: 1.06(d, J=4.88Hz, 3H), 1.85-2.1(m, 2H), 3.6-3.9(m, 1H), 4.75-5.05(m, 4H), 5.6-5.87(m, 1H), 7.19(brs, 2H), 8.43(s, 1H),	DMSO + Et ₃ N
157	NH ₂	 Trans-form	CF	Pale yellow powder	≥259 (decomposed)	[DMSO-d ₆]: 2.83(brs, 2H), 3.5-3.75(m, 2H), 3.8-3.95(m, 1H), 4.75-5.1(m, 1H), 5.6-5.8(m, 1H), 7.21(brs, 2H), 8.45(s, 1H)	DMSO + Et ₃ N
158	NH ₂	 Isomer B	CF	Yellow powder	≥224 (decomposed)	[DMSO-d ₆]: 2.45-2.75(m, 1H), 3.63(brs, 3H), 3.92(brs, 2H), 4.50(brs, 1H), 4.68(brs, 1H), 4.8-5.1(m, 4H), 5.6-5.8(m, 1H), 7.24(br, 2H), 8.48(s, 1H)	DMSO + Et ₃ N
159	NH ₂	 Isomer A	CF	Yellow powder	≥222 (decomposed)	[DMSO-d ₆]: 2.5-2.7(m, 1H), 3.75-4.0(m, 1H), 4.52(s, 1H), 4.69(s, 1H), 4.75-5.05(m, 4H), 5.6-5.8(m, 1H), 7.23(brs, 1H), 8.47(s, 1H)	DMSO + Et ₃ N
160	H ₂ N		CF	Yellow powder	249-251	[CDCl ₃ + DMSO-d ₆]: 0.25-0.5(m, 4H), 1.52-1.68(m, 1H), 2.66(s, 4H), 3.24(s, 4H), 4.85-5.1(m, 4H), 5.55-5.75(m, 1H), 6.53(brs, 2H), 8.50(s, 1H)	DMSO + Et ₃ N

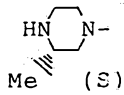
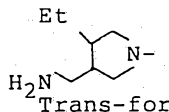
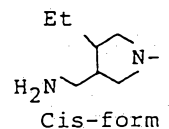
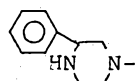
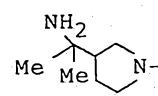
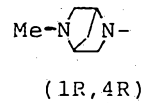
[Table 5-4]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
161	H ₂ N		CF	Yellow powder	257-259	[DMSO-d ₆ + D ₂ O]: 2.46(t,2H), 2.54(s,4H), 3.29(s,4H), 3.52(brs,2H), 4.40(brs,1H), 4.80-5.05(m,4H), 4.65-4.8(m,1H), 7.27(brs,2H), 8.55(s,1H)	DMSO + Et ₃ N
162	H ₂ N	 Isomer B	CF	Yellow powder	224-228	[DMSO-d ₆]: 2.25-2.45(m,1H), 3.28(s,3H), 3.8-3.95(m,1H), 4.75-5.0(m,4H), 4.6-4.75(m,1H), 7.12(brs,2H), 8.45(s,1H)	DMSO + Et ₃ N
163	H ₂ N		CF	Yellow powder	≥223 (colored & decomposed)	[DMSO-d ₆]: 2.9-3.6(m,7H), 4.37(d,J=5.4Hz,1H), 4.55(d,J=5.4Hz,1H), 4.8-5.0(m,4H), 5.65-5.8(m,1H), 7.37(brs,2H), 8.55(s,1H)	DMSO + Et ₃ N
164	H ₂ N		CF	Yellow powder	245-248	[DMSO-d ₆]: 1.05-1.3(m,6H), 1.65-1.9(m,4H), 2.2-2.35(m,1H), 2.59(s,4H), 3.26(s,4H), 4.8-5.05(m,4H), 5.65-5.8(m,1H), 7.31(brs,2H), 8.53(s,1H)	DMSO + Et ₃ N
165	H ₂ N		CF	Yellow powder	193-194	[CDCl ₃]: 2.62(s,4H), 3.24(d,J=6.35Hz,2H), 3.39(s,4H), 4.85-5.1(m,4H), 5.65-5.85(m,1H), 6.2-6.4(m,1H), 6.55-6.7(m,3H), 7.2-7.5(m,5H), 8.56(s,1H)	DMSO + Et ₃ N
166	H ₂ N		CF	Yellow powder	178-196	[CDCl ₃]: 2.62(s,2H), 3.05(s,3H), 3.39(s,2H), 3.75(s,1H), 4.87-5.1(m,4H), 5.65-5.8(m,1H), 6.53(brs,2H), 7.4-7.61(m,3H), 7.7-7.9(m,4H), 8.55(s,1H)	DMSO + Et ₃ N

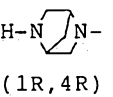
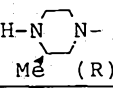
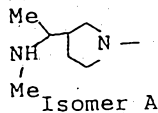
[Table 5-5]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
167	H ₂ N		CF	Yellow powder	225-230	[DMSO-d ₆]: 0.97(d, J=5.37Hz, 3H), 2.77(s, 2H), 3.05-3.2(m, 1H), 3.2-3.45(m, 4H), 4.75-4.9(m, 2H), 4.92-5.0(m, 2H), 5.65-5.81(m, 1H), 7.30(brs, 2H), 8.54(s, 1H)	DMSO + Et ₃ N
168	H ₂ N		CF	Yellow powder	256-260	[CDCl ₃]: 1.09(d, J=6.34Hz, 6H), 2.75-2.9(m, 2H), 2.95-3.1(m, 2H), 3.2-3.35(m, 2H), 4.89-5.1(m, 4H), 5.65-5.8(m, 1H), 6.54(brs, 2H), 8.57(s, 1H)	DMSO + Et ₃ N
169	H ₂ N		CF	Yellow powder	247-250	[CDCl ₃ + DMSO-d ₆]: 1.12(s, 9H), 2.70(s, 4H), 3.38(s, 4H), 4.9-4.98(m, 2H), 5.0-5.1(m, 2H), 5.67-5.8(m, 1H), 6.65(brs, 2H), 8.57(s, 1H)	DMSO + Et ₃ N
170	H ₂ N		CF	Yellow powder	218-225	[CDCl ₃ + DMSO-d ₆]: 0.94(t, J=7Hz, 3H), 1.45-1.65(m, 2H), 2.3-2.4(m, 2H), 2.58(s, 4H), 3.39(s, 4H), 4.83-5.15(m, 4H), 5.7-5.9(m, 1H), 6.69(brs, 2H), 8.59(s, 1H)	DMSO + Et ₃ N
171	H ₂ N		CF	Yellow powder	211-216	[CDCl ₃ + DMSO-d ₆]: 1.10(d, J=6.35Hz, 3H), 2.35(s, 3H), 2.75-2.85(m, 1H), 2.95-3.05(m, 1H), 3.2-3.5(m, 3H), 4.85-5.1(m, 4H), 5.65-5.85(m, 1H), 6.64(brs, 2H), 8.60(s, 1H)	DMSO + Et ₃ N
172	H ₂ N		CF	Yellow needle crystals	244-251	[CDCl ₃]: 1.35-1.5(m, 1H), 1.65-1.9(m, 3H), 2.05-2.25(m, 2H), 2.3-2.45(m, 1H), 2.95-3.2(m, 3H), 3.3-3.55(m, 3H), 4.86-5.15(m, 4H), 5.6-5.8(m, 1H), 6.54(brs, 2H), 8.57(s, 1H)	DMSO + Et ₃ N

[Table 5-6]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
173	H ₂ N	 (S)	CF	Yellow powder	≥300	[DMSO-d ₆]: 1.23(d, J=6.34Hz, 3H), 3.15-3.5(m, 7H), 4.8-5.0(m, 4H), 5.65-5.8(m, 1H), 7.37(brs, 2H), 8.57(s, 1H)	DMSO + Et ₃ N
174	H ₂ N	 Trans-form	CF	Yellow powder	178-185	[DMSO-d ₆]: 0.75-0.97(m, 3H), 1.2-1.4(m, 1H), 1.5-1.7(m, 1H), 1.8-2.0(m, 1H), 2.1-2.25(m, 1H), 4.75-5.05(m, 4H), 5.6-5.8(m, 1H), 7.05-7.35(m, 2H), 8.45(s, 1H)	DMSO + Et ₃ N
175	H ₂ N	 Cis-form	CF	Yellow powder	174-179	[DMSO-d ₆]: 0.8-1.0(m, 3H), 1.25-1.55(m, 2H), 2.05-2.3(m, 1H), 2.9-3.1(m, 1H), 3.5-3.8(m, 2H), 4.7-5.1(m, 4H), 5.55-5.8(m, 1H), 7.15(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
176	H ₂ N		CF	Yellow powder	224-230	[DMSO-d ₆]: 2.85-3.1(m, 2H), 3.8-3.9(m, 1H), 4.8-5.0(m, 4H), 5.7-5.9(m, 1H), 7.2-7.5(m, 7H), 8.56(s, 1H)	DMSO + Et ₃ N
177	H ₂ N		CF	Yellow powder	129-138	[DMSO-d ₆]: 1.07(s, 6H), 1.6-1.75(m, 1H), 1.8-1.95(m, 1H), 2.0-2.2(m, 1H), 4.72-5.0(m, 4H), 5.6-5.75(m, 1H), 7.17(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
178	H ₂ N	 (1R, 4R)	CF	Yellow powder	≥272 (colored & decomposed)	[CDCl ₃ + DMSO-d ₆]: 1.85(d, J=9.27Hz, 1H), 2.00(d, J=9.28Hz, 1H), 2.43(s, 3H), 2.8-3.0(m, 2H), 3.4-3.6(m, 2H), 3.75-3.9(m, 1H), 4.51(brs, 1H), 4.85-5.15(m, 4H), 5.6-5.8(m, 1H), 6.51(brs, 2H), 8.47(s, 1H)	Pyridine DBU

[Table 5-7]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
179	H ₂ N	 (1R, 4R)	CF	Yellow solid	≥300	[DMSO-d ₆]: 1.4-1.8(m, 2H), 3.00(brs, 2H), 3.85(brs, 1H), 4.54(s, 1H), 4.65-5.0(m, 4H), 5.65-5.8(m, 1H), 7.20(brs, 2H), 8.42(s, 1H)	Pyridine DBU
180	H ₂ N	 (R)	CF	Yellow powder	≥260 (decomposed)	[DMSO-d ₆]: 1.25(d, J=5.86Hz, 3H), 4.8-5.05(m, 4H), 5.65-5.85(m, 1H), 7.3-7.45(m, 2H), 8.57(s, 1H)	DMSO + Et ₃ N
181	H ₂ N	 Isomer A	CF	Yellow powder	185-191	[DMSO-d ₆]: 1.18(d, J=6.3Hz, 3H), 1.5-1.85(m, 1H), 2.05-2.25(m, 1H), 2.3-2.45(m, 1H), 2.5(s, 3H), 3.0-3.2(m, 1H), 3.4-3.85(m, 4H), 4.75-5.1(m, 4H), 5.6-5.85(m, 1H), 7.18(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N

Example 13

Ethyl 6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 33)

4 g of ethyl 2,4,5-trifluorobenzoylacetate, 4.06 ml of ethyl orthoformate and 6.9 ml of acetic anhydride were reacted at 130°C for 1.5 hours. Volatile components were distilled off under reduced pressure, followed by the addition of 50 ml of benzene. At room temperature, 1.3 g of 3-aminooxetane were added and stirred at the same temperature for 15 hours. The solvent was distilled off. Hexane was added and a solid thus formed was collected by filtration (about 4.2 g).

4.2 g of the solid and 1.76 g of potassium carbonate were reacted at 110°C for 15 minutes in 20 ml of dimethylformamide. The solvent was distilled off and the residue was extracted with 50 ml of chloroform. The chloroform extract was washed with water and then dried over MgSO_4 . The solvent was thereafter distilled off. Hexane was added and the resulting solid was collected by filtration, whereby 2.13 g of the title compound was obtained as a yellow solid. Melting point: 177-178°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.42(t, $J=7\text{Hz}$, 3H), 4.41(q, $J=7\text{Hz}$, 2H), 5.0-5.2(m, 4H),
5.4-5.6(m, 1H), 6.9-7.0(m, 1H), 8.2-8.4(m, 1H),
8.59(s, 1H).

Example 14

6,7-Difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 34)

2.13 g of Compound No. 33 was dissolved under heat in the mixture of 30 ml of THF and 30 ml of ethanol, to which 10 ml of water and 15 ml of 10% aq. sodium carbonate solution were added. They were reacted under reflux for 1.5 hours. After the organic solvents were distilled off, the residue was acidified with 1N-HCl and the resultant solid was collected by filtration. The solid was successively washed with 3 ml portions of water, ethanol and ether, whereby 1.58 g of the title compound was obtained as a pale red solid.

Melting point: 255-256°C.

¹H-NMR (DMSO-d₆) δ:

4.9-5.2(m, 4H), 5.8-5.9(m, 1H), 7.8-8.0(m, 1H),
8.2-8.4(m, 1H), 8.89(s, 1H).

Example 15

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 35)

80 mg of Compound No. 34 and 100 mg of 1-methylpiperazine were reacted at 80°C for 1 hour in 1 ml of dimethylformamide. After the solvent was distilled off, 3 ml of ethanol was added to the residue so that the latter was

solidified. In addition, 10 ml of hexane were added and the solid was collected by filtration. The solid was successively washed with 5 ml of ethanol, 1 ml of chloroform and 5 ml of hexane, whereby 68 mg of the title compound was
5 obtained as a yellow solid.

Melting point: 178-180°C.

¹H-NMR (DMSO-d₆) δ:

2.27(s,3H), 2.4-2.6(s,4H), 3.3-3.4(s,4H),
4.9-5.2(m,4H), 5.9-6.1(m,1H), 6.84(d,J=7.3Hz,1H),
10 7.94(d,J=13.6Hz,1H), 8.71(s,1H).

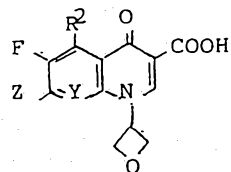
Example 16:

Compound Nos. 36-42 and Compound Nos. 182-188, which are shown in Table 6, were obtained in a similar manner to
Example 15.

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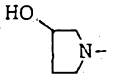
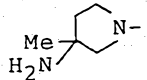
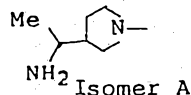
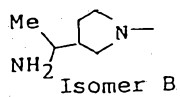
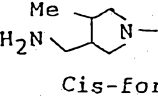
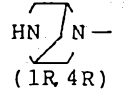
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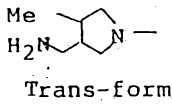
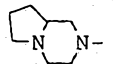
[Table 6-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
36	H		CH	Yellow solid	129-130	[DMSO-d ₆]: 2.8-2.9(brs,4H), 3.2-3.3(brs,4H), 4.9-5.2(m,4H), 5.9-6.0(m,1H), 6.81(d,J=7Hz,1H), 7.92(d,J=13.7Hz,1H), 8.71(s,1H)	DMSO
37	H		CH	Pale yellow solid	249-251	[DMSO-d ₆]: 1.7-2.1(m,2H), 3.1-3.8(m,5H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 6.3(d,J=7.3Hz,1H), 7.82(d,J=14.7Hz,1H), 8.60(s,1H)	DMSO + Et ₃ N
38	H		CH	Pale yellow solid	148-149	[DMSO-d ₆]: 1.7-2.2(m,2H), 2.6-2.8(m,1H), 2.8-3.0(m,2H), 3.2-3.9(m,4H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 6.31(d,J=6Hz,1H), 7.85(d,J=14.1Hz,1H), 8.61(s,1H)	DMSO + Et ₃ N
39	H		CH	Colorless solid	246-247	[DMSO-d ₆]: 1.7-1.9(m,2H), 2.23(s,6H), 2.7-2.9(m,1H), 3.2-3.8(m,4H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 6.34(d,J=7Hz,1H), 7.82(d,J=14.2Hz,1H), 8.61(s,1H)	DMF + Et ₃ N
40	H		CH	Yellow solid	209-210	[DMSO-d ₆]: 1.7-2.3(m,2H), 2.7-3.0(m,7H), 3.1-3.3(m,2H), 3.4-3.9(m,4H), 4.9-5.2(m,4H), 5.7-5.9(m,1H), 7.15(d,J=7Hz,1H), 7.84(d,J=13.6Hz,1H), 8.59(s,1H)	DMF + Et ₃ N
41	H		CH	Pale yellow solid	≥270 (decomposed)	[DMSO-d ₆]: 3.7-4.0(m,3H), 4.25-4.4(m,2H), 4.8-5.2(m,4H), 5.8-5.9(m,1H), 6.18(d,J=7.3Hz,1H), 7.81(d,J=12.7Hz,1H), 8.62(s,1H)	DMSO + Et ₃ N

[Table 6-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
42	H		CH	Pale yellow solid	293-295	[DMSO-d ₆]: 1.8-2.1(m,2H), 3.4-3.8(m,4H), 4.3-4.5(m,1H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 6.32(d,J=7.3Hz,1H), 7.83(d,J=14.1Hz,1H), 8.60(s,1H)	DMF + Et ₃ N
182	H		CH	Colorless powder	281-284	[DMSO-d ₆]: 1.28(s,3H), 1.8-1.9(m,2H), 3.5-3.9(m,2H), 4.9-5.15(m,4H), 5.8-5.95(m,1H), 6.28(d,J=7.33Hz,1H), 7.81(d,J=14.65Hz,1H), 8.60(s,1H)	DMSO + Et ₃ N
183	H	 Isomer A	CH	Yellow powder	≥233 (colored & decomposed)	[DMSO-d ₆]: 1.27(d,J=5.86Hz,3H), 1.7-1.9(m,1H), 2.1-2.3(m,1H), 2.4-2.6(m,1H), 4.96(brs,2H), 5.11(brs,2H), 5.87(brs,1H), 6.32(brs,1H), 7.81(d,J=14.16Hz,1H), 8.59(s,1H)	DMSO + Et ₃ N
184	H	 Isomer B	CH	Yellow powder	≥248 (colored & decomposed)	[DMSO-d ₆]: 1.25(d,J=5.86Hz,3H), 1.65-1.9(m,1H), 2.05-2.2(m,1H), 2.3-2.5(m,1H), 3.5-3.8(m,4H), 4.87-5.07(m,2H), 5.1-5.28(m,2H), 5.75-5.9(m,1H), 6.27(d,J=6.8Hz,1H), 7.85(d,J=14.2Hz,1H), 8.59(s,1H)	DMSO + Et ₃ N
185	H	 Cis-form	CH	Pale yellow powder	178-183	[DMSO-d ₆]: 1.00(brs,3H), 2.7-3.1(m,2H), 4.98(brs,2H), 5.13(brs,2H), 5.7-5.95(m,1H), 6.30(s,1H), 7.83(d,J=14.16Hz,1H), 8.59(s,1H)	DMSO + Et ₃ N
186	H	 (1R, 4R)	CH	Pale yellow solid	281-286	[DMSO-d ₆]: 1.65-1.9(m,2H), 2.85-3.05(m,2H), 3.5-3.85(m,3H), 4.69(s,1H), 4.9-5.18(m,4H), 5.8-5.95(m,1H), 6.37(d,J=7.8Hz,1H), 7.85(d,J=14.16Hz,1H), 8.61(s,1H)	Pyridine DBU

[Table 6-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
187	H	 Trans-form	CH	Pale yellow powder	204-208	[DMSO-d ₆]: 1.12(s,3H), 2.16(brs,2H), 2.75-2.95(m,1H), 3.05-3.15(m,1H), 3.75-3.96(m,2H), 4.97(brs,2H), 5.15(brs,2H), 5.75-5.95(m,1H), 6.28(brs,1H), 7.85(d,J=14.16Hz,1H), 8.59(s,1H)	DMSO + Et ₃ N
188	H	 N-	CH	Pale yellow powder	185-190	[CDCl ₃]: 1.4-2.0(m,4H), 2.1-2.3(m,2H), 2.4-2.6(m,1H), 2.65-2.8(m,1H), 3.0-3.25(m,3H), 3.6-3.83(m,2H), 5.05-5.3(m,4H), 5.55-5.7(m,1H), 6.52(d,J=6.84Hz,1H), 8.05(d,J=13.2Hz,1H), 8.67(s,1H)	DMSO + Et ₃ N

Example 17

6-Fluoro-7-(imidazol-1-yl)-8-methoxy-1-(oxetan-3-yl)-
1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound
No. 43)

5 158 mg of Compound No. 8 and 290 mg of sodium
methoxide (28% methanol solution) were reacted under reflux
for 15 hours in 5 ml of methanol. After the solvent was
distilled off, 3 ml of water was added. The pH of the
resultant mixture was adjusted to about 6-7 with 20% acetic
10 acid and the resultant solid was collected by filtration.
The solid was washed successively with small amounts of
water and ethanol, whereby 70 mg of the title compound was
obtained as pale yellow powder.

Melting point: 152-154°C.

15 $^1\text{H-NMR}$ (DMSO- d_6) δ :

3.34(s,3H), 4.8-5.1(m,4H), 5.9-6.1(m,1H),
7.23(brs,1H), 7.55(brs,1H), 8.03(brs,1H),
8.09(d,J=10Hz,1H), 8.84(s,1H).

Example 18

20 6,8-Difluoro-7-(3-methylaminopyrrolidin-1-yl)-1-(oxetan-
3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid
(Compound No. 44)

80 mg of Compound No. 3, 69 mg of 3-methylamino-
pyrrolidine dihydrochloride and 162 mg of triethylamine were
25 reacted at 80°C for 1 hour in 0.5 ml of DMSO. 2 ml of

ethanol and 10 ml of hexane were added, and the resulting solid was collected by filtration. The solid was washed successively with 3 ml of ethanol and 3 ml of hexane, whereby 68 mg of the title compound was obtained as a pale yellow solid.

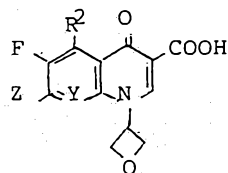
Melting point: 252-255°C.

¹H-NMR (DMSO-d₆) δ:

1.7-2.1(m, 2H), 2.29(s, 3H), 3.1-3.9(m, 5H),
4.85-5.05(m, 4H), 5.8-5.9(m, 1H), 7.74(d, J=14Hz, 1H),
8.63(s, 1H).

Example 19:

Compound Nos. 45-59, Compound No. 85, Compound No. 112 and Compound Nos. 118-147, which are shown in Table 7, were obtained in a similar manner to Example 18.



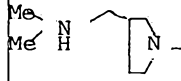
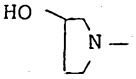
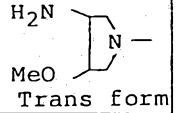
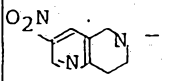
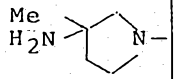
[Table 7-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
45	H		CF	Pale yellow solid	235-237	[DMSO-d ₆]: 1.03(t, J=7Hz, 3H), 1.7-2.1(m, 2H), 2.45-2.7(m, 2H), 3.2-3.9(m, 5H), 4.85-5.1(m, 4H), 5.75-5.9(m, 1H), 7.74(d, J=15.1Hz, 1H), 8.64(s, 1H)	DMSO + Et ₃ N
46	H		CF	Pale yellow solid	266-271	[DMSO-d ₆]: 1.6-2.2(m, 2H), 2.44(s, 3H), 2.3-3.8(m, 7H), 4.9-5.1(m, 4H), 5.8-5.9(m, 1H), 7.75(d, J=15Hz, 1H), 8.65(s, 1H)	DMSO + Et ₃ N
47	H		CF	Pale yellow solid	251-253.5	[DMSO-d ₆]: 1.22(t, J=7Hz, 3H), 1.7-2.2(m, 2H), 2.4-2.7(m, 3H), 2.9-3.1(m, 2H), 3.2-3.9(m, 4H), 4.9-5.1(m, 4H), 5.8-6.0(m, 1H), 7.8(d J=15Hz, 1H), 8.65(s, 1H)	DMSO + Et ₃ N
48	H		CF	Pale yellow solid	233-237	[DMSO-d ₆]: 3.7-3.85(m, 1H), 3.9-4.1, 4.45-4.6(m, 4H), 4.9-5.05(m, 4H), 5.7-5.95(m, 1H), 7.73(d, J=12.2Hz, 1H), 8.63(s, 1H)	DMSO + Et ₃ N
49	NH ₂		CF	Pale yellow solid	178-180	[DMSO-d ₆]: 3.85-4.0(m, 1H), 4.05-4.2, 4.45-4.55(m, 4H), 4.75-5.0(m, 4H), 5.6-5.75(m, 1H), 7.2(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
50	NH ₂		CF	Yellow powder	214-216	[DMSO-d ₆]: 1.65-2.0(m, 2H), 2.29(s, 3H), 3.1-3.8(m, 5H), 4.75-5.0(m, 4H), 5.6-5.75(m, 1H), 7.15(brs, 2H), 8.43(s, 1H)	DMSO + Et ₃ N

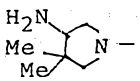
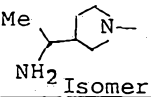
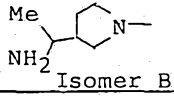
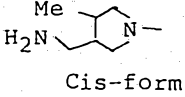
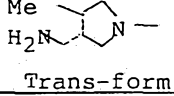
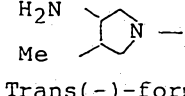
[Table 7-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
51	NH ₂		CF	Yellow powder	205-209	[DMSO-d ₆]: 1.06(t, J=7Hz, 3H), 1.7-2.1(m, 2H), 2.62-2.66(m, 2H), 3.1-3.9(m, 5H), 4.75-5.0(m, 4H), 5.6-5.75(m, 1H), 7.2(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
52	NH ₂		CF	Yellow solid	198-201	[DMSO-d ₆]: 1.55-2.15(m, 2H), 2.34(s, 3H), 2.55-2.7(m, 1H), 2.7-3.8(m, 6H), 4.75-5.0(m, 4H), 5.6-5.8(m, 1H), 7.15(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
53	NH ₂		CF	Yellow solid	175-178	[DMSO-d ₆]: 1.03(t, J=6.9Hz, 3H), 1.55-2.1(m, 2H), 2.25-2.4(m, 1H), 2.55-2.7(m, 2H), 3.0-3.8(m, 6H), 4.8-5.0(m, 4H), 5.6-5.8(m, 1H), 7.2(brs, 2H), 8.44(s, 1H)	DMSO + Et ₃ N
54	NH ₂		CF	Yellow solid	250-253	[DMSO-d ₆]: 4.0-4.1, 4.45-4.65(m, 5H), 4.75-5.0(m, 4H), 5.6-5.8(m, 1H), 7.2(brs, 2H), 8.43(s, 1H)	DMSO + Et ₃ N
55	NH ₂		CF	Yellow solid	217-220	[DMSO-d ₆]: 2.80(brs, 4H), 3.21(brs, 4H), 4.75-5.1(m, 4H), 5.65-5.8(m, 1H), 7.28(brs, 2H), 8.54(s, 1H)	DMSO
56	NH ₂		CF	Yellow solid	217-220	[DMSO-d ₆]: 2.05-2.4(m, 2H), 2.75(s, 6H), 3.6-4.0(m, 4H), 4.75-5.05(m, 4H), 5.6-5.8(m, 1H), 7.26(brs, 2H), 8.47(s, 1H)	DMSO + Et ₃ N

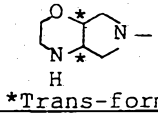
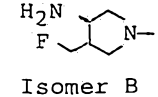
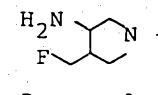
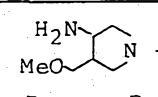
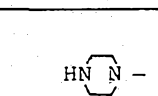
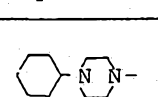
[Table 7-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
57	NH ₂		CF	Yellow solid	224-227	[DMSO-d ₆]: 1.6-2.2(m,2H), 2.5-2.6(m,1H), 2.74(s,6H), 3.1-3.2(m,2H), 3.4-3.9(m,4H), 4.75-5.0(m,4H), 5.6-5.8(m,1H), 7.2(brs,2H), 8.43(s,1H)	DMSO + Et ₃ N
58	NH ₂		CF	Yellow solid	248-250	[DMSO-d ₆ + D ₂ O]: 3.29(s,4H), 3.71(s,4H), 4.8-5.1(m,4H), 5.65-5.8(m,1H), 7.3(brs,2H), 8.54(s,1H)	DMF
59	NH ₂		CF	Yellow solid	260-262	[DMSO-d ₆]: 1.7-2.0(m,2H), 3.3-3.9(m,4H), 4.25-4.4(brs,1H), 4.75-5.1(m,5H), 5.6-5.8(m,1H), 7.16(brs,2H), 8.43(s,1H)	DMF + Et ₃ N
85	H	 Trans form	CF	Colorless solid	219-222	[DMSO-d ₆ + D ₂ O]: 3.30(s,3H), 3.3-4.2(m,6H), 4.8-5.1(m,4H), 5.7-5.9(m,1H), 7.75(d,J=13.7Hz,1H), 8.63(s,1H)	DMSO + Et ₃ N
112	H		CF	Pale yellow solid	≥230 (decomposed)	[DMSO-d ₆]: 2.7-3.9(m,4H), 4.3-4.8(m,2H), 4.8-5.2(m,4H), 5.7-6.0(m,1H), 7.92(d,J=12Hz,1H), 8.47(s,1H), 8.76(s,1H), 9.23(s,1H)	DMF + Et ₃ N
118	H		CF	Colorless powder	262-265	[DMSO-d ₆]: 1.25(s,3H), 1.75(brs,2H), 3.3-4.0(m,4H), 4.85-5.1(m,4H), 5.75-5.9(m,1H), 7.73(d,J=13.7Hz,1H), 8.62(s,1H)	DMSO + Et ₃ N

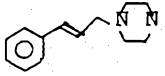
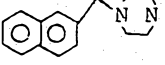
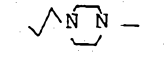
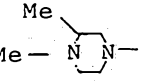
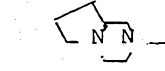
[Table 7-4]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
119	H		CF	Slightly yellow powder	colored from 160°C, decomposed at 183°C and above	[DMSO-d ₆]: 1.03(s,3H), 1.10(s,3H), 2.3-2.7(m,1H), 3.5-4.0(m,4H), 4.85-5.15(m,4H), 5.75-6.0(m,1H), 7.76(d,J=13.7Hz,1H), 8.66(s,1H)	DMSO + Et ₃ N
120	H	 Isomer A	CF	Yellow powder	215-218	[DMSO-d ₆]: 1.21(d,J=6.3Hz,3H), 1.6-1.8(m,1H), 2.1-2.4(m,2H), 3.1-3.9(m,4H), 4.8-5.1(m,4H), 5.7-5.9(m,1H), 7.75(d,J=14.1Hz,1H), 8.64(s,1H)	DMSO + Et ₃ N
121	H	 Isomer B	CF	Yellow powder	≥264°C (colored and decomposed)	[DMSO-d ₆]: 1.23(d,J=6.4Hz,3H), 1.5-1.7(m,1H), 1.9-2.4(m,2H), 3.1-3.8(m,4H), 4.8-5.05(m,4H), 5.7-5.9(m,1H), 7.75(d,J=14.1Hz,1H), 8.62(s,1H)	DMSO + Et ₃ N
122	H	 Cis-form	CF	Pale yellow powder	179-184	[DMSO-d ₆]: 0.95(d,J=6.8Hz,3H), 2.3-2.5(m,2H), 2.6-2.9(m,2H), 3.3-3.9(m,4H), 4.9-5.1(m,4H), 5.8-6.0(m,1H), 7.8(d,J=14Hz,1H), 8.65(s,1H)	DMSO + Et ₃ N
123	H	 Trans-form	CF	Pale yellow powder	125-133	[DMSO-d ₆]: 1.05(d,J=4.9Hz,3H), 1.9-2.1(m,2H), 2.6-3.0(m,2H), 3.0-3.9(m,4H), 4.9-5.1(m,4H), 5.8-6.0(m,1H), 7.8(d,J=14Hz,1H), 8.66(s,1H)	DMSO + Et ₃ N
124	H	 Trans(-)-form	CF	Slightly yellow powder	193-204	[DMSO-d ₆]: 1.06(d,J=4.4Hz,3H), 2.3-2.5(m,1H), 3.1-4.1(m,5H), 4.85-5.1(m,4H), 5.75-5.9(m,1H), 7.75(d,J=13.7Hz,1H), 8.65(s,1H)	DMSO + Et ₃ N

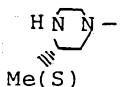
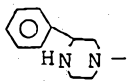
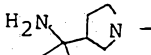
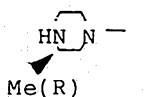
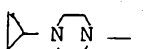
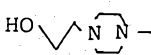
[Table 7-5]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
125	H	 *Trans-form	CF	Slightly yellow powder	231-238	[DMSO-d ₆]: 2.7-3.0(m,2H), 3.15-3.8(m,7H), 4.8-4.9(m,1H), 4.85-5.1(m,4H), 5.8-5.95(m,1H), 7.76(d,J=13.1Hz,1H), 8.66(s,1H)	DMSO + Et ₃ N
126	H	 Isomer B	CF	Slightly yellow powder	200-216	[DMSO-d ₆]: 2.2-2.5(m,1H), 3.1-4.05(m,5H), 4.4-4.8(m,2H), 4.85-5.2(m,4H), 5.75-5.95(m,1H), 7.76(d,J=14.2Hz,1H), 8.67(s,1H)	DMSO + Et ₃ N
127	H	 Isomer A	CF	Slightly yellow powder	211-218	[DMSO-d ₆]: 2.2-2.4(m,1H), 3.2-4.0(m,5H), 4.45-4.8(m,2H), 4.85-5.1(m,4H), 5.75-5.95(m,1H), 7.74(d,J=12.7Hz,1H), 8.66(s,1H)	DMSO + Et ₃ N
128	H	 Isomer B	CF	Slightly yellow powder	225-229	[DMSO-d ₆]: 2.3-2.45(m,1H), 3.28(s,3H), 3.2-4.0(m,7H), 4.8-5.1(m,4H), 5.75-5.9(m,1H), 7.71(d,J=12.7Hz,1H), 8.64(s,1H)	DMSO + Et ₃ N
129	H		CF	Slightly yellow powder	188-191	[DMSO-d ₆]: 2.9-3.6(m,7H), 4.5-4.75(m,2H), 4.9-5.2(m,4H), 5.85-6.0(m,1H), 7.90(d,J=11.2Hz,1H), 8.78(s,1H)	DMSO + Et ₃ N
130	H		CF	Slightly yellow powder	228-233	[CDCl ₃]: 1.0-1.4(m,6H), 1.8-2.0(m,4H), 2.2-2.4(m,1H), 2.73(s,4H), 3.41(s,4H), 4.95-5.25(m,4H), 5.8-6.0(m,1H), 7.93(d,J=11.7Hz,1H), 8.78(s,1H)	DMSO + Et ₃ N

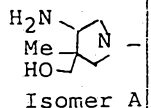
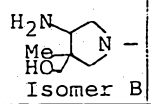
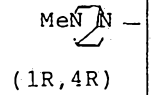
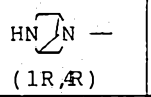
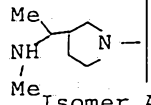
[Table 7-6]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
131	H		CF	Slightly yellow powder	190-201	[CDCl ₃]: 2.66(s,4H), 3.24(d,J=6.8Hz,1H), 3.42(s,4H), 5.0-5.2(m,4H), 5.75-6.0(m,1H), 6.2-6.4(m,1H), 6.57(d,J=16.1Hz,1H), 7.2-7.5(m,5H), 7.94(d,J=11.7Hz,1H), 8.75(s,1H)	DMSO + Et ₃ N
132	H		CF	Slightly yellow powder	143-153	[CDCl ₃]: 2.4-2.6(m,4H), 3.08(s,2H), 3.42(brs,3H), 3.77(s,1H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 7.5-8.0(m,7H), 8.75(s,1H)	DMSO + Et ₃ N
133	H		CF	Slightly yellow powder	153-159	[CDCl ₃ + DMSO-d ₆]: 1.44(s,9H), 2.6(brs,4H), 3.2(brs,4H), 4.95-5.2(m,4H), 5.8-6.0(m,1H), 7.96(d,J=11.3Hz,1H), 8.82(s,1H)	DMSO + Et ₃ N
134	H		CF	Slightly yellow powder	199-201	[CDCl ₃]: 0.95(t,J=7.3Hz,3H), 1.5-1.7(m,2H), 2.40(t,J=7.8Hz,2H), 2.61(brs,4H), 3.42(brs,4H), 4.9-5.2(m,4H), 5.8-5.95(m,1H), 7.95(dd,J=12Hz,J=1.6Hz), 8.76(s,1H)	DMSO + Et ₃ N
135	H		CF	Slightly yellow powder	165-168	[CDCl ₃]: 1.14(d,J=5.9Hz,3H), 2.39(s,3H), 2.3-2.5(m,2H), 2.85-3.0(m,1H), 3.1-3.6(m,4H), 4.9-5.2(m,4H), 5.8-5.95(m,1H), 7.95(d,J=9.8Hz,1H), 8.77(s,1H)	DMSO + Et ₃ N
136	H		CF	Slightly yellow powder	182-193	[CDCl ₃]: 1.35-1.6(m,1H), 1.7-2.0(m,3H), 2.1-2.3(m,1H), 2.35-2.5(m,1H), 2.95-3.2(m,3H), 3.3-3.6(m,3H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 7.94(d,J=11.7Hz,1H), 8.76(s,1H)	DMSO + Et ₃ N

[Table 7-7]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
137	H		CF	Slightly yellow powder	245-253	[DMSO-d ₆]: 1.26(d, J=5.9Hz, 3H), 3.0-3.6(m, 7H), 4.85-5.1(m, 4H), 5.8-5.95(m, 1H), 7.90(d, J=11.2Hz, 1H), 8.79(s, 1H)	DMSO + Et ₃ N
138	H		CF	Slightly yellow powder	128-133	[DMSO-d ₆]: 2.8-3.5(m, 6H), 3.85-3.95(m, 1H), 4.85-5.1(m, 4H), 5.85-6.0(m, 1H), 7.25-7.5(m, 5H), 7.87(d, J=12.2Hz, 1H), 8.78(s, 1H)	DMSO + Et ₃ N
139	H		CF	Slightly yellow powder	238-243	[DMSO-d ₆]: 1.07(s, 6H), 1.5-2.0(m, 2H), 2.05-2.2(m, 1H), 3.1-3.9(m, 4H), 4.85-5.1(m, 4H), 5.75-5.95(m, 1H)	DMSO + Et ₃ N
140	H		CF	Slightly yellow powder	Colored from 230°C, decomposed at 240°C and above	[DMSO-d ₆]: 1.24(d, J=6.3Hz, 3H), 3.0-3.6(m, 7H), 4.85-5.1(m, 4H), 5.8-6.0(m, 1H), 7.91(d, J=13.7Hz, 1H), 8.79(s, 1H), 7.73(d, J=14.2Hz, 1H), 8.63(s, 1H)	DMSO + Et ₃ N
141	H		CF	Colorless powder	211-215	[CDCl ₃]: 1.35-1.55(m, 4H), 1.6-1.8(m, 1H), 2.76(brs, 4H), 3.35(brs, 4H), 4.95-5.2(m, 4H), 5.8-5.95(m, 1H), 7.93(d, J=10.3Hz, 1H), 8.75(s, 1H)	DMSO + Et ₃ N
142	H		CF	Colorless powder	216-219	[CDCl ₃ + DMSO-d ₆]: 2.5-2.75(m, 6H), 3.41(brs, 4H), 3.6-3.8(m, 2H), 4.95-5.25(m, 4H), 5.8-6.0(m, 1H), 7.93(d, J=11.7Hz, 1H), 8.79(s, 1H)	DMSO + Et ₃ N

[Table 7-8]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
143	H	 Isomer A	CF	Slightly yellow powder	165-171	[DMSO-d ₆]: 1.10(s,3H), 3.2-4.1(m,7H), 4.8-5.1(m,4H), 5.7-6.0(m,1H), 7.76(d,J=13.7Hz,1H), 8.66(s,1H)	DMSO + Et ₃ N
144	H	 Isomer B	CF	Slightly yellow powder	150-154	[DMSO-d ₆]: 1.02(s,3H), 2.8-4.0(m,7H), 4.8-5.1(m,4H), 5.75-6.0(m,1H), 7.75(d,J=13.6Hz,1H), 8.67(s,1H)	DMSO + Et ₃ N
145	H	 (1R,4R)	CF	Pale yellow powder	≥260 °C (colored and decomposed)	[CDCl ₃ + DMSO-d ₆]: 1.87(d,J=9.77Hz,1H), 2.03(d,J=9.76Hz,1H), 2.44(s,3H), 2.8-3.0(m,2H), 3.47(brs,1H), 3.5-3.6(m,1H), 3.8-3.95(m,1H), 4.56(s,1H), 4.9-5.15(m,4H), 5.65-5.85(m,1H), 7.85(d,J=12.2Hz,1H), 8.66(s,1H)	pyridine DBU
146	H	 (1R,4R)	CF	Pale yellow powder	≥275 °C (decomposed)	[DMSO-d ₆]: 1.6-2.0(m,2H), 3.05(brs,2H), 4.61(brs,1H), 4.7-5.1(m,4H), 5.6-5.9(m,1H), 7.75(d,J=13Hz,1H), 8.61(s,1H)	Pyridine DBU
147	H	 Isomer A	CF	Pale yellow powder	215-220	[DMSO-d ₆]: 1.00(d,J=6.4Hz,3H), 1.6-1.75(m,1H), 2.0-2.25(m,2H), 2.30(s,1H), 4.9-5.1(m,4H), 5.8-5.95(m,1H), 7.73(d,J=14.6Hz,1H), 8.64(s,1H)	DMSO + Et ₃ N Pyridine DBU

Example 20

Ethyl 7-chloro-6-fluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxo-1,8-naphthylidine-3-carboxylate (Compound No. 60)

8.4 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate,
5 7.5 ml of ethyl orthoformate and 12.7 ml of acetic an-
hydride were reacted at 130°C for 2 hours. Volatile com-
ponents were distilled off under reduced pressure, followed
by the addition of 30 ml of dichloromethane and 2.56 g of
3-aminooxetane. They were reacted at room temperature for
10 1.5 hours. The solvent was distilled off. 100 ml of
hexane was added to the resulting solid, followed by the
collection of the solid by filtration. 10.5 g of the solid
thus collected was dissolved in 140 ml of tetrahydrofuran,
to which 1.21 g of sodium hydride (content: 60%) was added
15 by portions under ice cooling over 30 minutes. They were
reacted further at room temperature for 30 minutes and then
under reflux for additional 1 hour. Tetrahydrofuran was
distilled off, followed by the extraction with 100 ml of
chloroform. The chloroform layer was washed successively
20 with 30 ml of 1N-HCl and 50 ml of water, and then dried
over MgSO₄. Chloroform was distilled off. To the residue
were added 50 ml of hexane and 50 ml of ether, so that the
residue was solidified. The solid thus obtained was ground
and collected by filtration. 5.15 g of the title compound
25 were obtained as pale yellow powder.

Melting point: 163-166°C.

¹H-NMR (CDCl₃) δ:

1.43(t, J=7Hz, 3H), 4.40(q, J=7Hz, 2H),
4.97(t, J=6.8Hz, 2H), 5.20(t, J=7.4Hz, 2H),
5 5.95-6.15(m, 1H), 8.47(d, J=8.3Hz, 1H), 8.81(s, 1H).

Example 21

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(oxetan-3-yl)-1,4-dihydro-4-oxo-1,8-naphthylidene-3-carboxylic acid
(Compound No. 61)

10 200 mg of Compound No. 60, 64 mg of N-methylpiperazine and 65 mg of triethylamine were reacted under reflux for 1.5 hours in 5 ml of chloroform. Volatile components were distilled off and to the residue were added 5 ml of ethanol, 3 ml of 10% aq. sodium carbonate solution and 2 ml of
15 water. They were reacted under reflux for 1.5 hours. The solvent was distilled off. 20% acetic acid was added to the residue to adjust the pH to about 6. The resulting solid was collected by filtration and successively washed with ethanol and ether, whereby 13 mg of the title compound was
20 obtained as a colorless solid.

Melting point: 235-236.5°C.

¹H-NMR (CDCl₃) δ:

2.36(s, 3H), 2.5-2.6(m, 4H), 3.8-3.9(m, 4H),
4.95-5.2(m, 4H), 5.8-6.0(m, 1H), 8.1(d, J=13.2Hz, 1H),
25 8.76(s, 1H).

Example 22

Compound Nos. 62-73, Compound No. 88 and Compound Nos. 189-196, which are shown in Table 8, were obtained in a similar manner to Example 21.

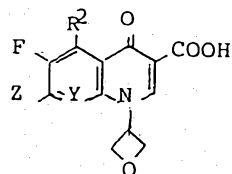
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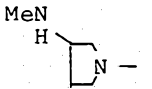
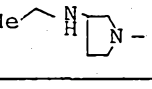
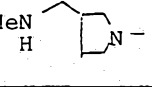
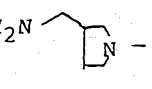
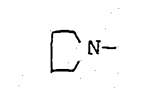
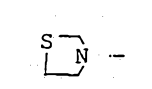
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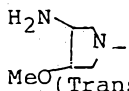
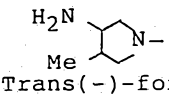
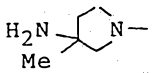
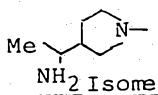
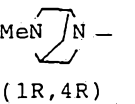
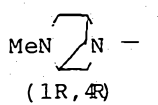
[Table 8-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
62	H		N	Colorless solid	≥280 °C (decomposed)	[DMSO-d ₆]: 2.83(brs, 4H), 3.73(brs, 4H), 4.9-5.1(m, 4H), 5.75-5.95(m, 1H), 8.08(d, J=13.2Hz, 1H), 8.68(s, 1H)	CHCl ₃
63	H		N	Colorless solid	249.5-251	[CDCl ₃]: 3.86(s, 8H), 5.0-5.2(m, 4H), 5.85-6.0(m, 1H), 8.14(d, J=13.2Hz, 1H), 8.78(s, 1H)	CHCl ₃
64	H		N	Colorless solid	265-266.5	[CDCl ₃]: 2.7-2.9(m, 4H), 4.05-4.2(m, 4H), 5.0-5.2(m, 4H), 5.8-5.95(m, 1H), 8.14(d, J=13.2Hz, 1H), 8.77(s, 1H)	CHCl ₃
65	H		N	Pale yellow solid	≥300 (decomposed)	[DMSO-d ₆]: 1.6-2.1(m, 2H), 3.1-4.0(m, 5H), 4.9-5.1(m, 4H), 5.7-5.85(m, 1H), 7.96(d, J=13.2Hz, 1H), 8.55(s, 1H)	CHCl ₃
66	H		N	Pale yellow solid	225-228	[DMSO-d ₆]: 1.7-2.3(m, 2H), 2.22(s, 6H), 2.7-2.9(m, 1H), 3.2-4.05(m, 4H), 4.9-5.15(m, 4H), 5.7-5.9(m, 1H), 7.99(d, J=13.7Hz, 1H), 8.60(s, 1H)	CHCl ₃ + Et ₃ N
67	H		N	Pale yellow solid	259-261	[DMSO-d ₆]: 1.8-2.1(m, 2H), 3.55-4.0(m, 4H), 4.35-4.5(m, 1H), 4.9-5.1(m, 4H), 5.7-5.9(m, 1H), 7.98(d, J=13.2Hz, 1H), 8.59(s, 1H)	CHCl ₃ + Et ₃ N

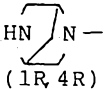
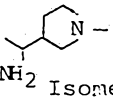
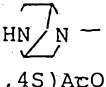
[Table 8-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
68	H		N	Pale yellow solid	≥280°C (decomposed)	[DMSO-d ₆]: 1.8-2.1(m,2H), 2.30(s,3H), 3.1-4.0(m,5H), 4.9-5.1(m,4H), 5.7-5.85(m,1H), 7.98(d,J=13.2Hz,1H), 8.58(s,1H)	CHCl ₃ + Et ₃ N
69	H		N	Pale yellow solid	210-213	[DMSO-d ₆]: 1.05(t,J=7Hz,3H), 1.8-2.2(m,2H), 2.5-2.7(m,2H), 3.2-3.9(m,5H), 4.9-5.1(m,4H), 5.7-5.9(m,1H), 7.97(d,J=13.2Hz,1H), 8.57(s,1H)	CHCl ₃ + Et ₃ N
70	H		N	Colorless solid	232-236	[DMSO-d ₆]: 1.6-2.2(m,2H), 2.30(s,3H), 2.3-2.6(m,1H), 3.2-4.0(m,6H), 4.9-5.1(m,4H), 5.7-5.9(m,1H), 7.97(d,J=13.2Hz,1H), 8.58(s,1H)	CHCl ₃ + Et ₃ N
71	H		N	Pale yellow solid	216-218	[DMSO-d ₆]: 1.6-2.2(m,2H), 2.5-2.7(m,1H), 3.0-4.0(m,6H), 4.9-5.1(m,4H), 5.7-5.9(m,1H), 7.95(d,J=13.2Hz,1H), 8.56(s,1H)	CHCl ₃ + Et ₃ N
72	H		N	Pale yellow solid	286-289	[CDCl ₃]: 1.9-2.1(brs,4H), 3.6-4.0(m,4H), 5.0-5.2(m,4H), 5.75-5.9(m,1H), 7.98(d,J=12.7Hz,1H), 8.64(s,1H)	CHCl ₃
73	H		N	Pale yellow solid	264-267	[CDCl ₃ + DMSO-d ₆]: 3.21(t,J=6.3Hz,2H), 4.05-4.2(m,2H), 4.88(s,2H), 5.0-5.2(m,4H), 5.8-6.0(m,1H), 8.10(d,J=12.2Hz,1H), 8.77(s,1H)	CHCl ₃

[Table 8-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
88	H	 (Trans-form)	N	Colorless powder	155.5-156.5	[DMSO-d ₆ + D ₂ O]: 3.32(s,3H), 3.3-4.1(m,6H), 4.85-5.2(m,4H), 5.7-5.9(m,1H), 7.98(d,J=12.2Hz,1H), 8.59(s,1H)	CHCl ₃ + Et ₃ N
189	H	 Trans(-)-form	=N-	Pale yellow powder	colored from 230 °C, decomposed at 280 °C and above	[DMSO-d ₆]: 1.03(s,3H), 2.15-2.35(m,1H), 4.85-5.2(m,4H), 5.7-5.9(m,1H), 7.93(d,J=13.2Hz,1H), 8.55(s,1H)	CHCl ₃ + Et ₃ N
190	H	 Me	=N-	Pale yellow powder	266-269	[DMSO-d ₆]: 1.29(s,3H), 1.7-1.9(m,2H) 4.85-5.1(m,4H), 5.7-5.9(m,1H), 7.93(d,J=13.2Hz,1H), 8.55(s,1H)	CHCl ₃ + Et ₃ N
191	H	 NH ₂ Isomer A	=N-	Pale yellow powder	234-237	[DMSO-d ₆]: 1.05(d,3H), 2.05-2.2(m,2H), 2.75-2.9(m,1H), 4.95-5.05(m,4H), 5.75-5.85(m,1H), 8.0(d,J=13Hz,1H), 8.32(s,1H)	CHCl ₃ + Et ₃ N
192	H	 (1R,4R)	=N-	Colorless powder	≥270 °C (colored and decomposed)	[DMSO-d ₆]: 1.8-2.05(m,2H), 2.35(s,3H), 2.6-2.7(m,1H), 2.85-2.95(m,1H), 3.6-3.9 (m,2H), 4.85-5.15(m,5H), 5.6-5.75(m,1H), 8.02(d,J=12.7Hz,1H), 8.60(s,1H)	CHCl ₃ + DBU
193	H	 (1R,4R)	CH	Pale yellow powder	256-260	[DMSO-d ₆]: 2.0-2.25(m,2H), 2.65(s,3H) 3.4-3.8(m,4H), 4.03(brs,1H), 4.82(s,1H), 4.9-5.2(m,4H), 5.8-6.0(m,1H), 6.46(d,J=6.35Hz,1H) 7.89(d,J=13.57Hz,1H), 8.65(s,1H)	Pyridine DBU

[Table 8-4]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
194	H	 (1R, 4R)	=N-	Pale yellow powder	≥300	[DMSO-d ₆]: 1.7-1.9(m, 2H), 2.9-3.1(m, 2H), 3.77(brs, 1H), 4.9-5.2(m, 5H), 5.7-5.9(m, 1H), 7.98(d, J=12.2Hz, 1H), 8.59(s, 1H)	CHCl ₃ + DBU
195	H	 Isomer B	=N-	Pale yellow powder	218-223	[DMSO-d ₆]: 1.23(brs, 3H), 1.6-1.85(m, 1H), 1.96-2.2(m, 1H), 2.2-2.42(m, 1H), 3.0-3.25(m, 1H), 4.85-5.2(m, 4H), 5.7-5.9(m, 1H), 7.95(d, J=12.7Hz, 1H), 8.58(s, 1H)	CHCl ₃ + Et ₃ N
196	H	 (1S, 4S)ArOH	H	Yellow powder	≥275 (decomposed)	[DMSO-d ₆]: 1.65-1.95(m, 2H), 1.88(s, 3H), 2.8-3.1(m, 2H), 3.5-3.9(m, 2H), 4.70(s, 1H), 4.8-5.15(m, 4H), 5.8-5.95(m, 1H), 6.36(d, J=6.83Hz, 1H), 7.83(d, J=14.2Hz, 1H), 8.60(s, 1H)	CHCl ₃ + Et ₃ N

Example 23

Ethyl 6,7-difluoro-8-methoxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 74)

10.8 g of ethyl 2-chloro-4,5-difluoro-3-methoxy-
5 benzoylacetate, 9.4 ml of ethyl orthoformate and 15.7 ml of acetic anhydride were reacted at 130°C for 3 hours. After volatile components were distilled off, 40 ml of benzene and 29.2 g of 3-aminooxetane were added at room temperature. They were reacted at the same temperature for 50 minutes.
10 After the solvent was distilled off, 30 ml of ether was added to the residue so that the latter was solidified. The resultant solid was ground and then collected by filtration, whereby 10.4 g of a white solid was obtained. The solid was dissolved in 500 ml of tetrahydrofuran, to which 1.28 g of
15 sodium hydride (content: 60%) was added. They were stirred for 3 days under gently refluxed. The solvent was distilled off, and 300 ml of water was added to the residue, followed by extraction with chloroform (200 ml x 3 times). The organic layers were dried over MgSO_4 and distilled off. To
20 the residue was added 100 ml of ether so that the latter was solidified. The solid thus formed was ground and then collected by filtration, whereby 3.8 g of the title compound was obtained as a pale yellow solid.

Melting point: 195-198°C.

¹H-NMR (CDCl₃) δ:

1.41(t, J=7.05Hz, 3H), 4.03(d, J=1.95Hz, 3H), 4.41(q, J=7.05Hz, 2H), 4.85-5.2(m, 4H), 5.8-6.0(m, 1H), 8.0-8.1(m, 1H), 8.67(s, 1H).

5 Example 24

6,7-Difluoro-8-methoxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 75)

2.7 g of Compound No. 74 was reacted under reflux for 20 minutes in a liquid mixture which consisted of 110 ml of tetrahydrofuran and 40 ml of 2N sodium hydroxide solution. Tetrahydrofuran was distilled off and the remaining aqueous solution was rendered acidic (about pH 6) with 20% acetic acid. The resultant solid was collected by filtration and then successively washed with 10 ml of water, 20 ml of ethanol and 30 ml of ether, whereby 1.97 g of the title compound was obtained as a colorless solid.

Melting point: 178-179°C.

¹H-NMR (CDCl₃) δ:

4.10(d, J=2.48Hz, 3H), 4.85(m, 4H), 5.9-6.1(m, 1H), 8.05-8.15(m, 1H), 8.87(m, 1H).

Example 25

7-(3-Aminopyrrolidin-1-yl)-6-fluoro-8-methoxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 76)

100 mg of Compound No. 75 and 86 g of 3-amino-

pyrrolidine were reacted at 80°C for 30 minutes in 1 ml of DMSO. After the reaction mixture was cooled, 2 ml of ethanol and 20 ml of ether were added and the resultant mixture was stirred. The supernatant was removed by decantation. The residue was solidified with 5 ml of ethanol, followed by grinding. The solid was collected by filtration and washed with 5ml of ethanol, whereby 42 mg of the title compound was obtained as a colorless solid. Melting point: 199-202°C.

10 ¹H-NMR (DMSO-d₆ + D₂O) δ:

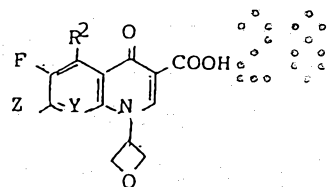
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4.7-5.1(m,4H), 5.8-6.0(m,1H), 7.65(d,J=14.6Hz,1H),
8.58(s,1H).

Example 26

15 Compound Nos. 77-84, 86, 87, 89-96, 101-103, 106 and 107, which are shown in Table 9, were obtained in a similar manner to Example 25.

20

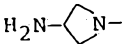
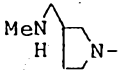
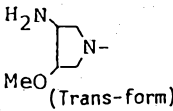
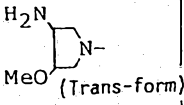
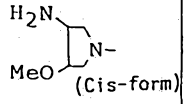
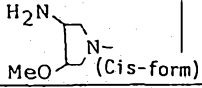
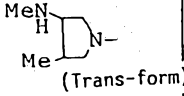
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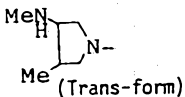
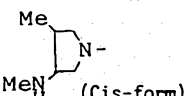
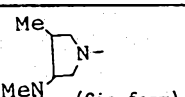
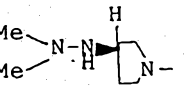
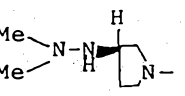
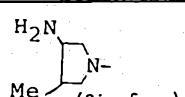
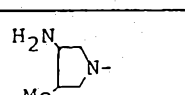
[Table 9-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
77	H		C-OMe	Pale yellow solid	212.5-214	[CDCl ₃]: 1.7-2.3(m,2H), 2.33(s,6H), 2.6-2.8(m,1H), 3.50(s,3H), 3.5-4.0(m,4H), 4.7-5.3(m,4H), 5.8-6.0(m,1H), 7.85(d,J=13.7Hz,1H), 8.63(s,1H)	DMF + Et ₃ N
78	H		C-OMe	Yellow solid	237-239	[CDCl ₃]: 1.99(brs,4H), 3.48(s,3H), 3.61(brs,4H), 4.85-5.2(m,4H), 5.8-5.95(m,1H), 7.83(d,J=13.7Hz,1H), 8.60(s,1H)	DMF
79	H		C-OMe	Yellow solid	147-149	[DMSO-d ₆]: 1.22(t,J=6.3Hz,3H), 1.7-2.2(m,2H), 2.4-2.7(m,1H), 2.8-3.1(m,4H), 3.48(s,3H), 3.3-3.8(m,4H), 4.7-5.1(m,4H), 5.8-6.0(m,1H), 7.71(d,J=13.7Hz,1H), 8.61(s,1H)	DMSO + Et ₃ N
80	H		C-OMe	Yellow solid	225-227	[DMSO-d ₆]: 1.7-2.1(m,2H), 3.45(s,3H), 3.2-4.0(m,4H), 4.2-4.45(m,1H), 4.6-5.2(m,4H), 5.8-6.0(m,1H), 7.67(d,J=13.7Hz,1H), 8.59(s,1H)	DMF + Et ₃ N
81	H		C-OMe	Pale yellow solid	157-159	[DMSO-d ₆]: 2.82(brs,4H), 3.22(brs,4H), 3.67(s,3H), 4.65-5.1(m,4H), 5.8-6.0(m,1H), 7.76(d,J=12.7Hz,1H), 8.66(s,1H)	DMSO
82	H		C-OMe	Colorless solid	182-184	[DMSO-d ₆]: 1.03(t,J=7.6Hz,3H), 1.7-2.1(m,2H), 2.4-2.6(m,2H), 3.46(s,3H), 3.0-3.8(m,5H), 4.7-5.1(m,4H), 5.8-6.0(m,1H), 7.68(d,J=13.2Hz,1H), 8.60(s,1H)	DMSO + Et ₃ N

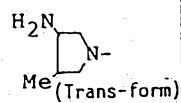
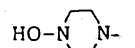
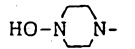
[Table 9-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
83	H		C-OMe	Pale yellow solid	200.5-203	[DMSO-d ₆]: 3.50(s,3H), 3.7-4.0, 4.35-4.55(m,5H), 4.7-5.1(m,4H), 5.8-6.0(m,1H), 7.68(d,J=13.7Hz,1H), 8.59(s,1H)	DMSO + Et ₃ N
84	H		C-OMe	Colorless solid	202-204	[DMSO-d ₆]: 1.5-2.2(m,2H), 2.30(s,3H), 3.49(s,3H), 2.3-3.8(m,7H), 4.6-5.1(m,4H), 5.8-6.0(m,1H), 7.68(d,J=14.2,Hz,1H), 8.61(s,1H)	DMSO + Et ₃ N
86	-NH ₂	 (Trans-form)	CF	Pale yellowish green solid	161-164	[CDCl ₃ + DMSO-d ₆]: 3.43(s,3H), 3.2-4.2(m,6H), 4.8-5.2(m,4H), 5.6-5.8(m,1H), 6.6-6.9(br,2H), 8.52(s,1H)	DMSO + Et ₃ N
87	H	 (Trans-form)	CH	Gray solid	132-133	[DMSO-d ₆ + D ₂ O]: 3.33(s,3H), 3.2-4.1(m,6H), 4.8-5.2(m,4H), 5.8-6.0(m,1H), 6.2-6.4(m,1H), 7.83(d,J=13.6Hz,1H), 8.61(s,1H)	DMSO + Et ₃ N
89	H	 (Cis-form)	CF	Pale yellow solid	191-195	[DMSO-d ₆]: 3.45(s,3H), 3.2-3.9(m,6H), 4.8-5.1(m,4H), 5.75-5.9(m,1H), 7.73(d,J=13.6Hz,1H), 8.64(s,1H)	DMSO + Et ₃ N
90	-NH ₂	 (Cis-form)	CF	Pale yellow solid	183-187	[DMSO-d ₆]: 3.34(s,3H), 3.1-3.9(m,6H), 4.75-5.0(m,4H), 5.6-5.8(m,1H), 7.1-7.3(br,2H), 8.44(s,1H)	DMSO + Et ₃ N
91	H	 (Trans-form)	CF	Pale yellow solid	252-254	[DMSO-d ₆]: 0.97(d,J=6.84Hz,3H), 2.29(s,3H), 2.2-2.4(m,1H), 3.0-3.9(m,5H), 4.8-5.1(m,4H), 5.7-5.9(m,1H), 7.72(d,J=13.7Hz,1H), 8.64(s,1H)	DMSO + Et ₃ N

[Table 9-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
92	-NH ₂	 (Trans-form)	CF	Pale yellow solid	197-201	[DMSO-d ₆]: 0.96(d, J=6.84Hz, 3H), 2.29(s, 3H), 2.2-2.4(m, 1H), 3.0-3.9(m, 5H), 4.7-5.0(m, 4H), 5.6-5.8(m, 1H), 7.1-7.3(br, 2H), 8.43(s, 1H)	DMSO + Et ₃ N
93	H	 (Cis-form)	CF	Pale yellow solid	256-258	[DMSO-d ₆]: 1.03(d, J=6.34Hz, 3H), 1.95-2.1(m, 1H), 2.31(s, 3H), 2.6-4.0(m, 5H), 4.8-5.1(m, 4H), 5.7-5.9(m, 1H), 7.74(d, J=13.7Hz, 1H), 8.65(s, 1H)	DMSO + Et ₃ N
94	-NH ₂	 (Cis-form)	CF	Pale yellow solid	203-206	[DMSO-d ₆]: 1.03(d, J=6.35Hz, 3H), 1.9-2.1(m, 1H), 2.31(s, 3H), 2.6-3.9(m, 5H), 4.7-5.0(m, 4H), 5.6-5.8(m, 1H), 7.0-7.3(br, 2H), 8.43(s, 1H)	DMSO + Et ₃ N
95	H	 (Trans-form)	CF	Pale yellow solid	150-151.5	[DMSO-d ₆ + D ₂ O]: 1.9-2.3(m, 2H), 2.57(s, 6H), 3.0-3.9(m, 5H), 4.8-5.1(m, 4H), 5.7-5.9(m, 1H), 7.78(d, J=13.5Hz, 1H), 8.66(s, 1H)	DMSO + Et ₃ N
96	-NH ₂	 (Trans-form)	CF	Yellow solid	242-245	[DMSO-d ₆]: 2.0-2.4(m, 2H), 2.79(s, 6H), 2.9-3.9(m, 5H), 4.7-5.0(m, 4H), 5.6-5.8(m, 1H), 7.1-7.3(br, 2H), 8.47(s, 1H)	DMSO + Et ₃ N
101	-NH ₂	 (Cis-form)	CF	Yellow solid	217-220	[DMSO-d ₆]: 1.10(d, J=6.3Hz, 3H), 2.0-2.2(m, 1H), 2.8-4.2(m, 5H), 4.75-5.1(m, 4H), 5.6-5.8(m, 1H), 7.1-7.4(br, 2H), 8.45(s, 1H)	DMSO + Et ₃ N
102	H	 (Trans-form)	CF	Pale yellow solid	227-230	[CDCl ₃ + DMSO-d ₆]: 1.13(d, J=6.84Hz, 3H), 2.2-2.45(m, 1H), 3.4-4.1(m, 5H), 4.85-5.1(m, 4H), 5.75-5.95(m, 1H), 7.76(d, J=13.7Hz, 1H), 8.69(s, 1H)	DMSO + Et ₃ N

[Table 9-4]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
103	-NH ₂		CF	Pale yellow solid	234-238	[DMSO-d ₆]: 0.98(d, J=6.83Hz, 3H), 2.05-2.25(m, 1H), 3.1-3.8(m, 5H), 4.75-5.1(m, 4H), 5.6-5.8(m, 1H), 7.05-7.3(br, 2H), 8.42(s, 1H)	DMSO + Et ₃ N
106	H		CF	Pale yellow solid	242-245	[DMSO-d ₆]: 2.5-3.5(m, 8H), 4.8-5.1(m, 4H), 5.8-6.0(m, 1H), 7.86(d, J=12.2Hz, 1H), 8.76(s, 1H)	DMSO + Et ₃ N
107	-NH ₂		CF	Yellow solid	224-227	[DMSO-d ₆]: 2.5-3.5(m, 8H), 4.7-5.0(m, 4H), 5.6-5.8(m, 1H), 7.2-7.4(br, 2H), 8.54(s, 1H)	DMSO + Et ₃ N

Example 27

7-(Cis-3-amino-4-methylpyrrolidin-1-yl)-6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid trifluoroacetic acid salt (Compound No. 97)

200 mg of Compound No. 3, 160 mg of cis-3-t-butoxy-carbonylamino-4-methylpyrrolidine and 150 mg of triethylamine were reacted at 80°C for 1 hour in 3 ml of DMF. DMF was distilled off and ether was added to the residue. The resultant solid was collected by filtration. The solid was dissolved in 10 ml of chloroform, followed by the addition of 2 ml of trifluoroacetic acid under ice cooling. They were reacted at the same temperature for 10 minutes and then at room temperature for further 40 minutes. Volatile components were distilled off. To the residue were added 2 ml of ethanol and 30 ml of hexane. The resultant mixture was stirred and the supernatant was removed by decantation. To the oily residue was added 5 ml of ethanol so that the latter was solidified. The solid thus formed was ground and collected by filtration, whereby 150 mg of the title compound was obtained as a yellow solid.

Melting point: 225-227°C.

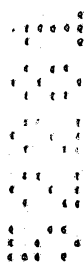
¹H-NMR (DMSO-d₆) δ:

1.14(d, J=6.35Hz, 3H), 2.25-2.4(m, 1H), 3.0-4.1(m, 5H),
4.8-5.2(m, 4H), 5.7-6.0(m, 1H), 7.76(d, J=14.2Hz, 1H),
8.67(s, 1H).

Example 28

Compound Nos. 98-100 and 197-214, which are shown in Table 10, were obtained in a similar manner to Example 27.

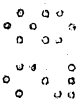
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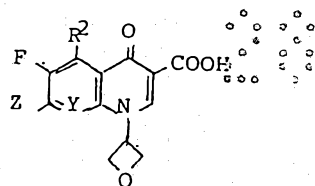


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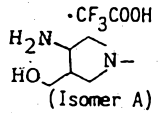
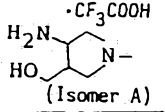
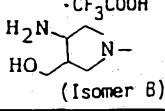
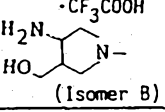
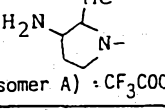
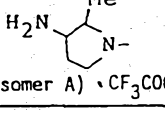
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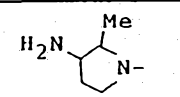
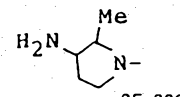
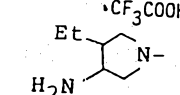
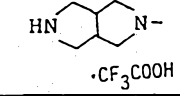
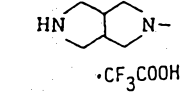
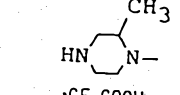
[Table 10-1]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
98	NH ₂	 •CF ₃ COOH (Cis-form)	CF	Yellow solid	229-234	[DMSO-d ₆]: 1.12(d, J=6.35Hz, 3H), 2.2-2.4(m, 1H), 3.1-4.1(m, 5H), 4.7-5.0(m, 4H), 5.6-5.8(m, 1H), 7.1-7.3(br, 2H), 8.46(s, 1H)	DMF + Et ₃ N
99	H	 •CF ₃ COOH (Trans-form)	CF	Pale Yellow solid	220-224	[DMSO-d ₆]: 1.10(brs, 3H), 2.4-2.7(m, 1H), 3.1-4.2(m, 5H), 4.8-5.2(m, 4H), 5.7-6.0(m, 1H), 7.78(d, J=13.2Hz, 1H), 8.66(s, 1H)	DMF + Et ₃ N
100	-NH ₂	 •CF ₃ COOH (Trans-form)	CF	Yellow solid	237-240.5	[DMSO-d ₆]: 1.08(d, J=5.86Hz, 3H), 2.4-2.6(m, 1H), 3.2-4.2(m, 5H), 4.7-5.1(m, 4H), 5.6-5.8(m, 1H), 7.1-7.5(br, 2H), 8.45(s, 1H)	DMF + Et ₃ N
197	H	 •CF ₃ COOH (1S, 4S)	≡N-	Pale yellow solid	202-207	[DMSO-d ₆]: 1.9-2.2(m, 2H), 3.94(s, 2H), 4.53(s, 1H), 4.95-5.2(m, 4H), 5.17(s, 1H), 5.7-5.9(m, 1H), 8.15(d, J=12.2Hz, 1H), 8.65(s, 1H), 9.1-9.6(br, 2H)	Pyridine + DBU
198	H	 •CF ₃ COOH (1S, 4S)	CF	Pale yellow solid	240-243	[DMSO-d ₆]: 1.85-2.25(m, 2H), 3.5-3.7(m, 2H), 3.85-4.0(m, 1H), 4.47(s, 1H), 4.82(s, 1H), 4.85-5.1(m, 4H), 5.75-5.95(m, 1H), 7.83(d, J=14.2Hz, 1H), 8.67(s, 1H), 9.10(brs, 2H)	Pyridine + DBU
199	H ₂ N	 •CF ₃ COOH (1S, 4S)	CF	Pale yellow solid	234-237	[DMSO-d ₆]: 1.8-2.0(m, 1H), 2.05-2.2(m, 1H), 3.45-3.6(m, 1H), 3.8-4.0(m, 1H), 4.44(s, 1H), 4.6-5.1(m, 4H), 5.55-5.8(m, 1H), 7.29(brs, 2H), 8.46(s, 1H), 8.6-9.2(br, 2H)	Pyridine + DBU

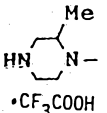
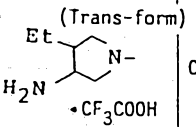
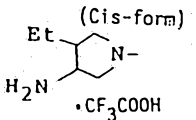
[Table 10-2]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
200	H	 (Isomer A)	CF	Slightly yellow powder	168-175	[DMSO-d ₆]: 2.3-2.55(m,1H), 3.55(bris,2H), 4.85-5.05(m,4H), 5.75-6.0(m,1H), 7.81(d,J=13.7Hz,1H), 8.22(bris,3H), 8.68(s,1H)	DMSO + Et ₃ N
201	H ₂ N	 (Isomer A)	CF	Pale yellow powder	221-224	[DMSO-d ₆]: 2.35-2.5(m,1H), 3.54(bris,2H), 3.69(bris,2H) 4.75-5.1(m,4H), 5.6-5.8(m,1H), 8.20(bris,3H) 8.48(s,1H)	DMSO + Et ₃ N
202	H	 (Isomer B)	CF	Pale yellow powder	197-201	[DMSO-d ₆]: 2.55-2.7(m,1H), 4.0-4.15(m,1H), 4.8-5.05(m,4H), 5.75-5.9(m,1H), 7.80(d,J=13.67Hz,1H), 8.04(bris, 3H), 8.68(s,1H)	DMSO + Et ₃ N
203	H ₂ N	 (Isomer B)	CF	Yellow powder	224-248	[DMSO-d ₆]: 2.52-2.7(m,1H), 3.9-4.1(m,1H), 4.75-5.0(m,4H), 5.6-5.8(m,1H), 6.9-7.6(br,2H), 8.04(bris,3H), 8.47(s,1H)	DMSO + Et ₃ N
204	H	 (Isomer A)	CF	Pale yellow powder	203-208	[DMSO-d ₆]: 1.13(d,J=5.86Hz,3H), 2.0-2.35(m,2H), 4.3-4.5(m,1H), 4.85-5.1(m,4H), 5.8-6.0(m,1H), 7.87(d,J=12.7Hz,1H), 8.16(bris,3H), 8.72(s,1H)	DMSO + Et ₃ N
205	H ₂ N	 (Isomer A)	CF	Yellow powder	228-231	[DMSO-d ₆]: 1.11(d,J=6.84Hz,3H), 2.0-2.38(m,2H) 3.8-4.1(m,2H), 4.3-4.45(m,1H), 4.75-5.1(m,4H), 5.6-5.9(m,1H), 7.1-7.5(br,2H), 8.13(bris,3H), 8.51(s,1H)	DMSO + Et ₃ N

[Table 10-3]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
206	H	 (Isomer B) • CF ₃ COOH	CF	Pale yellow powder	160-178	[DMSO-d ₆]: 1.19(d, J=5.86Hz, 3H), 1.85-2.05(m, 1H), 2.25-2.4(m, 1H), 3.45-3.6(m, 2H), 4.1-4.3(m, 1H), 4.85-5.1(m, 4H), 5.8-6.0(m, 1H), 7.85(d, J=13.7Hz, 1H), 8.35(brs, 3H), 8.71(s, 1H)	DMSO + Et ₃ N
207	H ₂ N	 (Isomer B) • CF ₃ COOH	CF	Yellow powder	230-234	[DMSO-d ₆]: 1.19(d, J=6.35Hz, 3H), 1.8-2.05(m, 1H), 2.2-2.4(m, 1H), 3.8-4.0(m, 1H), 4.05-4.25(m, 1H), 4.8-5.05(m, 4H), 5.65-5.8(m, 1H), 7.1-7.5(br, 2H), 8.31(brs, 3H), 8.50(s, 1H)	DMSO + Et ₃ N
208	H	 (Cis-form:Trans-form=1:1)	CF	Yellow powder	152-160	[DMSO-d ₆]: 0.8-1.0(m, 3H), 1.3-1.65(m, 2H), 2.1-2.3 and 2.3-2.45(m, 1H), 3.45-4.2(m, 5H), 4.87-5.1(m, 4H), 5.8-5.95(m, 1H), 7.79(d, J=13.7Hz, 1H), 8.05-8.35(m, 3H), 8.68 and 8.67(s, two peaks, 1H)	DMSO + Et ₃ N
209	H	 • CF ₃ COOH	CF	Pale yellow powder	246-248	[DMSO-d ₆]: 3.04(s, 4H), 3.4-3.75(m, 6H), 4.85-5.1(m, 4H), 5.8-5.95(m, 1H), 7.83(dd, J=11.2Hz, J=1.95Hz, 1H), 8.70(s, 1H), 8.97(brs, 2H)	DMSO + Et ₃ N
210	H ₂ N	 • CF ₃ COOH	CF	Yellow powder	250-252	[DMSO-d ₆]: 3.01(s, 4H), 3.35-3.75(m, 6H), 4.8-5.0(m, 4H), 5.6-5.8(m, 1H), 7.1-7.5(m, 2H), 8.47(s, 1H), 8.99(brs, 2H)	DMSO + Et ₃ N
211	H	 • CF ₃ COOH	CH	Pale yellow powder	131-140	[DMSO-d ₆]: 1.18(d, J=6.84Hz, 3H), 3.1-3.6(m, 7H), 4.95-5.1(m, 4H), 5.95-6.1(m, 1H), 7.00(d, J=6.84Hz, 1H), 8.00(d, J=12.7Hz, 1H), 8.77(s, 1H), 8.8-9.1(br, 1H), 9.1-9.4(br, 1H)	DMSO + Et ₃ N

[Table 10-4]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
212	H		CF	Yellow powder	198-205	[DMSO-d ₆]: 1.00(d, J=6.35Hz, 3H), 2.8-3.05(m, 1H) 3.1-3.4(m, 5H), 3.6-3.75(m, 1H), 4.85-5.1(m, 4H) 5.75-6.0(m, 1H), 7.97(d, J=12.2Hz, 1H), 8.83(s, 1H) 8.9-9.2(m, 2H)	DMSO + Et ₃ N
213	H ₂ N		CF	Yellow powder	259-264	[DMSO-d ₆]: 0.96(t, J=7.4Hz, 3H), 1.25-1.6(m, 2H) 2.3-2.45(m, 1H), 3.5-3.75(m, 2H), 3.8-3.9(m, 1H) 4.0-4.1(m, 1H), 4.75-5.0(m, 4H), 5.6-5.75(m, 1H), 7.25(brs, 2H), 8.47(s, 1H)	DMSO + Et ₃ N
214	H ₂ N		CF	Yellow powder	219-225	[DMSO-d ₆]: 0.94(t, J=7.3Hz, 3H), 1.25-1.45(m, 1H) 1.55-1.75(m, 1H), 2.05-2.2(m, 1H), 3.55-3.75(m, 1H) 3.8-4.0(m, 2H), 4.75-5.0(m, 4H), 5.6-5.8(m, 1H), 7.26(brs, 2H), 8.48(s, 1H)	DMSO + Et ₃ N

Example 29

7-(Trans-3-amino-4-methylpyrrolidin-1-yl)-6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (Compound No. 104)

5 70 mg of Compound No. 102 was suspended in 3 ml of ethanol. Under ice cooling, HCl-saturated ethanol was added little by little until the compound was completely dissolved. 3 ml of ether was added and the resultant solid was collected by filtration, whereby 60 mg of the title compound was obtained as a pale yellow solid.

Melting point: 188-190°C.

¹H-NMR (DMSO-d₆) δ:

1.10(d, J=6.83Hz, 3H), 2.4-2.6(m, 1H), 3.2-4.2(m, 5H),
4.8-5.1(m, 4H), 5.75-6.0(m, 1H), 7.79(d, J=13.7Hz, 1H),
15 8.67(s, 1H).

Example 30

5-Amino-7-(trans-3-amino-4-methylpyrrolidin-1-yl)-6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (Compound No. 105)

20 Using 100 mg of Compound No. 103, 90 mg of the title compound was obtained as a pale yellow solid by similar procedures to Example 29.

Melting point: ≥260°C (decomposed).

¹H-NMR (DMSO-d₆) δ:

1.08(d, J=6.84Hz, 3H), 2.4-2.6(m, 1H), 3.5-4.2(m, 5H),
4.7-5.1(m, 4H), 5.6-5.9(m, 1H), 7.2-7.4(br, 2H),
8.45(s, 1H).

5 Example 31

5-Amino-6,8-difluoro-7-(4-formimidoylpiperazin-1-yl)-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (Compound No. 108)

100 mg of Compound No. 55 and 100 mg of DBU were
10 stirred in 8 ml of ethanol, followed by the addition of 68
mg of benzyl formimidate hydrochloride at room temperature.
They were reacted for 1 hour. HCl-saturated ethanol was
added to the reaction mixture, so that the reaction mixture
was rendered weakly acidic. The resulting solid was col-
15 lected by filtration and washed with 5 ml of ether, whereby
83 mg of the title compound was obtained as a pale yellow
solid.

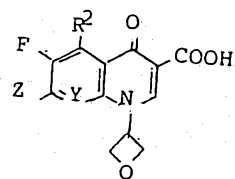
Melting point: 240-245°C.

¹H-NMR (DMSO-d₆) δ:

20 3.0-3.8(m, 8H), 4.8-5.1(m, 4H), 5.7-5.9(m, 1H),
7.3-7.6(br, 2H), 8.09(s, 1H), 8.56(s, 1H).

Example 32:

Compound Nos. 109-111 shown in Table 11 were obtained
in a similar manner to Example 31.



[Table 11]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
109	-NH ₂	 •HCl	CF	Yellow solid	232-235	[DMSO-d ₆]: 2.34(s,3H), 3.1-3.8(m,8H) 4.75-5.1(m,4H), 5.6-5.9(m,1H), 7.2-7.6(br,2H), 8.56(s,1H)	EtOH + DBU
110	-NH ₂	 •HCl	CF	Yellow solid	182-185	[DMSO-d ₆]: 1.7-2.2(m,2H), 3.3-3.9(m,5H), 4.7-5.1(m,4H), 5.6-5.8(m,1H), 7.1-7.3(br,2H), 7.60(s,1H), 8.41(s,1H)	EtOH + DBU
111	H	 •HCl	N	Colorless solid	270-273	[DMSO-d ₆]: 1.8-2.4(m,2H), 3.2-4.4(m,5H), 4.9-5.1(m,4H), 5.7-5.9(m,1H), 7.92(s,1H), 8.07(d,J=13.7Hz,1H), 8.61(s,1H)	EtOH

Example 33

5-Amino-7-((-)-trans-3-amino-4-methylpyrrolidin-1-yl)-
6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-
3-carboxylic acid (Compound No. 113)

- 5 (1) In the presence of triethylamine, 59 g of benzoyl
chloride was reacted at room temperature with 81.4 g of
trans-3-tert-butoxycarbonylamino-4-methylpyrrolidine in
methylene chloride, whereby 120 g of trans-3-tert-butoxy-
carbonylamino-4-methyl-1-benzoylpyrrolidine (a) was ob-
10 tained. Hydrochloric acid was then reacted at room tempera-
ture with 123 g of the compound (a) in ethanol, so that 83 g
of trans-3-amino-4-methyl-1-benzoylpyrrolidine (b) was ob-
tained. In methylene chloride, 68.4 g of (R)-(-)mandelic
acid was then reacted at room temperature with 83 g of the
15 compound (b) in the presence of 87.3 g of 1-hydroxybenzo-
triazole, 87.4 g of 1-ethyl-3-(3-dimethylaminopropyl)carbo-
diimide hydrochloride and 46.5 g of triethylamine. 34 g of
trans-3-(2-(R)-2-phenyl-2-hydroxyacetyl-amino)-4-methyl-1-
benzoylpyrrolidine diastereomer (A), (c) was obtained.
20 Acetic acid and hydrochloric acid were then reacted with the
compound (c) under reflux, whereby 16.8 g of (-)-trans-3-
amino-4-methylpyrrolidine dihydrochloride was obtained as a
colorless solid.

$[\alpha]_D^{20}$: -10.9° (c=0.53, MeOH)

25 $^1\text{H-NMR}$ (CD_3OD) δ :

1.22(d,J=7.3Hz,3H), 2.7-2.85(m,1H), 3.2-3.35(m,1H),
3.4-3.7(m,2H), 3.75-4.1(m,2H).

(2) Using 22 g of Compound No. 26, 16.5 g of the (-)-
trans-3-amino-4-methylpyrrolidine dihydrochloride obtained
5 in the above procedure (1), 43.4 g of triethylamine and 250
ml of DMSO, 22 g of the title compound was obtained as pale
yellow powder by similar procedures to Example 25. The pow-
der was dissolved under heat and reflux in 2 l of methanol.
After insoluble matter was filtered off, the methanol solu-
10 tion was allowed to cool down so that the powder was crys-
tallized. 15 g of the title compound was obtained as pale
yellow needle crystals.

Melting point: 270-275°C (decomposed).

¹H-NMR (DMSO-d₆) δ:

15 1.07(d,J=7.33Hz,3H), 2.4-2.6(m,1H), 3.4-4.1(m,5H),
4.7-5.1(m,4H), 5.6-5.8(m,1H), 7.1-7.4(brs,2H),
8.45(s,1H), 9.0-10.00(br,2H).

Example 34

20 5-Amino-7-((-)-trans-3-amino-4-methylpyrrolidin-1-yl)-
6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-
3-carboxylic acid methanesulfonic acid salt
(Compound No. 114)

In a liquid mixture consisting of 50 ml of ethanol
and 10 ml of water, 850 mg of Compound No. 113 and 934 mg
25 of methanesulfonic acid were stirred at 45°C for 20 minutes.

Insoluble matter was filtered off and 400 ml of ether was added to the filtrate. The resulting solid was collected by filtration and washed with ether, whereby 670 mg of the title compound was obtained as yellow powder.

5 Melting point: 242-245°C (decomposed).

¹H-NMR (DMSO-d₆) δ:

1.08(d, J=6.8Hz, 3H), 2.33(s, 3H), 2.5-2.6(m, 1H),
3.5-4.1(m, 5H), 4.75-5.0(m, 4H), 5.6-5.8(m, 1H),
7.1-7.4(br, 2H), 8.09(brs, 3H), 8.45(s, 1H).

10 Example 35

5-Amino-7-((-)-trans-3-amino-4-methylpyrrolidin-1-yl)-
6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-
3-carboxylic acid p-toluene sulfonic acid salt
(Compound No. 115)

15 500 mg of Compound No. 113 was suspended in 50 ml of
ethanol, followed by the addition of 30 ml of an ethanol
solution of 725 mg of p-toluenesulfonic acid monohydrate and
80 ml of chloroform. They were stirred at 45°C for 10
minutes. Insoluble matter was filtered off. The filtrate
20 was subjected to distillation under reduced pressure, so
that chloroform was removed. 400 ml of ether was added and
the resulting solid was collected by filtration, so that 584
mg of the title compound was obtained as yellow powder.

Melting point: 174-190°C.

25 ¹H-NMR (DMSO-d₆) δ:

1.08(d,J=6.8Hz,3H), 2.28(s,3H), 2.4-2.6(m,1H),
3.4-4.1(m,5H), 4.7-5.1 (m,4H), 5.6-5.8(m,1H), 7.1 and
7.47(d,J=7.8Hz,4H), 8.07(brs,3H), 8.45(s,1H).

Example 36

5 5-Amino-7-((-)-trans-3-amino-4-methylpyrrolidin-1-yl)-
6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-
3-carboxylic acid hydrochloride (Compound No. 116)

100 mg of Compound No. 113 was dissolved in a liquid
mixture consisting of 5 ml of water and 5 ml of ethanol,
10 followed by the addition of 3 ml of 1N-HCl under ice cool-
ing. They were stirred for 5 minutes. 30 ml of ether was
added and the resulting solid was collected by filtration,
whereby 70 mg of the title compound was obtained as yellow
powder.

15 Melting point: 265-275°C (decomposed).

¹H-NMR (DMSO-d₆) δ:

1.09(d,J=6.8Hz,3H), 2.4-2.6(m,1H), 3.5-4.1(m,5H),
4.7-5.1(m,4H), 5.6-5.8(m,1H), 7.1-7.4(br,2H),
8.45(s,1H), 8.3-8.7(brs,3H).

20 Example 37

5-Amino-7-((-)-trans-3-amino-4-methylpyrrolidin-1-yl)-
6,8-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-
3-carboxylic acid sulfuric acid salt (Compound No. 117)

1 g of Compound No. 113 was dissolved in a liquid mix-
25 ture consisting of 6 ml of water and 18 ml of ethanol, fol-

lowed by the addition of 1.53 g of sulfuric acid (97%) at 10-15°C. They were stirred for 10 minutes. The resulting solid was collected by filtration, washed with ethanol (10 ml, twice) and ether (10 ml, twice), whereby 1.08 g of the title compound was obtained as a pale yellow solid. Melting point: $\geq 290^\circ\text{C}$ (colored and decomposed).

$^1\text{H-NMR}$ (DMSO-d_6) δ :

1.09(d, $J=6.8\text{Hz}$, 3H), 2.5-2.7(m, 1H), 3.5-4.1(m, 5H),
4.7-5.1(m, 4H), 5.6-5.8(m, 1H), 7.1-7.4(br, 2H),
7.9-8.2(br, 3H), 8.45(s, 1H).

Example 38:

6-Fluoro-7-[(2S,4S)-2-methyl-4-aminopyrrolidin-1-yl]-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid [Compound No. 215]

100 g of Compound No. 34, 172 mg of (2S,4S)-2-methyl-4-benzyloxycarbonylaminopyrrolidine hydrochloride and 172 mg of triethylamine were reacted at 80°C for 2.5 hours in 2 ml of dimethylformamide. After the solvent was distilled off, the residue was subjected to column chromatography on silica gel (chloroform/methanol = 10/1) and the corresponding fractions were collected. The solvent was distilled off and the residue was dissolved in 60 ml of methanol. 100 mg of palladium/carbon was added to the solution. A reaction was then conducted for 2 days under hydrogen gas. After the catalyst was filtered off, the filtrate was distilled. The

residue was solidified with 5 ml of ethanol and then ground, so that 35 mg of the title compound was obtained as a pale yellow solid.

Melting point: $\geq 217^{\circ}\text{C}$ (decomposed).

5 ^1H -NMR (DMSO- d_6) δ :

1.18(s,3H), 1.95-2.15(m,1H), 2.25-2.5(m,1H),
3.99(brs,1H), 4.85-5.2(m,4H), 5.8-6.05(m,1H),
6.55(brs,1H), 7.91(d, $J=13.67\text{Hz}$,1H), 8.65(s,1H).

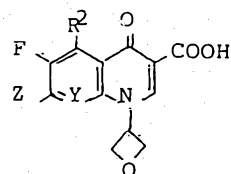
Example 39:

10 Compound Nos. 216 and 217 shown in Table 12 were obtained in a similar manner to Example 38.

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[Table 12]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
216	H		CF	Pale yellow powder	170-174	[DMSO-d ₆]: 1.05-1.15(m,3H), 1.6-1.8(m,1H), 2.3-2.45(m,1H), 3.55-3.7(m,1H), 4.87-5.10(m,4H), 5.8-5.95(m,1H), 7.75(d,J=13Hz,1H), 8.7(s,1H)	DMSO + Et ₃ N
217	H ₂ N		CF	Yellow powder	180-189	[DMSO-d ₆]: 1.12(s,3H), 1.8-2.0(m,1H), 2.2-2.45(m,1H), 2.95-3.15(m,1H), 4.8-5.1(m,4H), 5.65-5.8(m,1H), 7.31(brs,2H), 8.49(s,1H)	DMSO + Et ₃ N

Example 40:

Ethyl 6,7-Difluoro-5-hydroxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate [Compound No. 218]

6.5 g of benzyl alcohol was dissolved in 150 ml of
5 benzene. While the resultant solution was cooled with
water, 2.4 g of sodium hydride (60%) was added and reacted.
To the reaction mixture was added 15 g of benzyl 2,3,4,6-
tetrafluorobenzoate, and stirred at room temperature for 1
hour. 3.6 g of acetic acid was added, followed by the
10 removal of the solvent by distillation. To the residue, 6.5
g of potassium hydroxide and 50 ml of water and 100 ml of
methanol were added. They were reacted at 50°C for 30
minutes. 6 g of acetic acid was added, followed by the
removal of the solvent by distillation. To the residue were
15 added 50 ml of benzene and 7% aq. potassium hydroxide solu-
tion. The resultant mixture was shaken, followed by separa-
tion into two layers. Concentrated hydrochloric acid was
added to the water layer so that the water layer was
rendered acidic. The thus-acidified water layer was ex-
20 tracted twice with 100 ml portions of chloroform. The ex-
tract was treated with anhydrous magnesium sulfate and the
solvent was distilled out. A solid thus formed was dis-
persed in n-hexane and then collected by filtration, whereby
4.7 g of 6-benzyloxy-2,3,4-trifluorobenzoic acid was ob-
25 tained as colorless powder.

After 4.6 g of the benzoic acid derivative was reacted with 3 ml of oxalyl chloride at room temperature for 1 hour in 20 ml of dichloromethane which had been added with a single droplet of dimethylformamide, excess reagents and solvent were distilled off. An acid chloride was thus obtained as an oily residue. Into a homogeneous solution which had been obtained reacting 390 mg of magnesium and 2.8 g of diethyl malonate in a liquid mixture consisting of 2.5 ml of ethanol and 20 ml of tetrahydrofuran and which was cooled at -40°C , a solution of the above acid chloride in 10 ml of tetrahydrofuran was added dropwise so that they were reacted. The temperature of the reaction mixture was allowed to rise to room temperature, followed by the distillation of the solvents. The residue was added with 2 ml of concentrated hydrochloric acid, 20 ml of water and 50 ml of chloroform, followed by separation into two layers. The solvent was distilled off from the chloroform layer. To the residue were added 0.5 g of p-toluenesulfonic acid monohydrate and 30 ml of water. They were reacted at about 100°C for 2 hours. The reaction mixture was allowed to cool to room temperature, followed by extraction with 50 ml of chloroform. The chloroform layer was washed with 5% aq. sodium hydrogencarbonate solution and was then treated with anhydrous magnesium sulfate, whereby ethyl 6-benzyloxy-2,3,4-trifluorobenzoylacetate was obtained as an oily

residue.

1.76 g of the ethyl benzoylacetate was dissolved in 15 ml of benzene, followed by the addition of 0.66 g of dimethylformamide dimethylacetal. They were reacted under 5 reflux for 45 minutes. The solvent was distilled off and to the residue was added 10 ml of dichloromethane and 0.5 g of 3-aminooxetane. They were reacted at room temperature for 45 minutes. The solvent was distilled off. To the residue was added 1 g of anhydrous potassium carbonate and 5 ml of 10 dimethylformamide, followed by a reaction at 100°C for 1 hour. After the reaction mixture was allowed to cool down, 40 ml of chloroform and 250 ml of water were added to the reaction mixture. The thus-prepared mixture was then allowed to separate into two layers. The chloroform layer 15 was washed with water and then treated with anhydrous magnesium sulfate. The solvent was distilled off. Crystals thus precipitated were dispersed in a liquid mixture of diisopropyl ether and chloroform and then collected by filtration, whereby 810 mg of ethyl 5-benzyloxy-6,7-difluoro-1-20 (oxetan-3-yl)-1,4-dihydro-4-oxoquinolin-3-carboxylate was obtained (m.p. 220-222°C).

1.62 g of the ethyl quinolonecarboxylate derivative and 250 mg of 10% palladium/carbon were added to a liquid mixture which consisted of 8 ml of dichloromethane, 8 ml of 25 methanol and 6 ml of acetic acid. The resultant mixture

was hydrogenated for 2 hours. After the catalyst was filtered off, the solvent was distilled off. A solid thus precipitated was dispersed in diisopropyl ether and then collected by filtration, whereby 1.13 g of the title compound was obtained as colorless powdery crystals.

Melting point: 242-246°C (decomposed).

$^1\text{H-NMR}$ (CDCl_3) δ :

1.42 (t, $J=7\text{Hz}$, 3H), 4.43 (q, $J=7\text{Hz}$, 2H), 4.98-5.22 (m, 4H),
5.40-5.42 (m, 1H), 6.28 (dd, $J=11\text{Hz}$, 6Hz, 1H), 8.59 (s, 1H).

10 Example 41:

6,7-Difluoro-5-hydroxy-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 219)

315 mg of Compound No. 218 was dissolved in 80 ml of tetrahydrofuran, followed by the addition of 5.8 g of a 10% aqueous solution of tetra-n-butylammonium hydroxide. They was reacted at 45°C for 1 hour. After 180 mg of acetic acid and 5 ml of water were added, tetrahydrofuran was distilled off. A solid thus precipitated was collected by filtration and then successively washed with ethanol and diisopropyl ether, whereby 212 mg of the title compound was obtained as colorless powdery crystals.

Melting point: 273-276°C.

$^1\text{H-NMR}$ (DMSO-d_6) δ :

4.90-5.18 (m, 4H), 5.70-5.85 (m, 1H), 7.17 (dd, $J=11\text{Hz}$, 6Hz, 1H), 8.79 (s, 1H).

Example 42:

6-Fluoro-5-hydroxy-1-(oxetan-3-yl)-7-(piperazin-1-yl)-
1,4-dihydro-4-oxoquinolin-3-carboxylic acid (Compound
No. 220)

5 In 500 mg of dimethylsulfoxide, 90 mg of Compound No.
219 and 90 mg of piperazine were reacted at 90°C for 15
minutes. After the reaction mixture was allowed to cool
down, 4 ml of diisopropyl ether was added. The resulting
mixture was shaken and the supernatant was decanted with an
10 oily precipitate left behind. This procedure was repeated
three times. To the final oily precipitate was added 1 ml
of ethanol. A precipitate thus formed was collected by fil-
tration and then washed successively with ethanol and di-
isopropyl ether, whereby 75 mg of the title compound was ob-
15 tained as pale yellow powder.

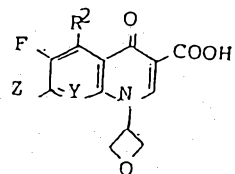
Melting point: 266-273°C (blackened).

¹H-NMR (DMSO-d₆) δ:

2.84-2.95(m,4H), 4.88-5.11(m,4H), 5.81-5.92(m,1H),
6.23(d,J=6Hz,1H), 8.64(s,1H).

20 Example 43:

Compound Nos. 221, 222, 224 and 225, which are shown
in Table 13, were obtained in a similar manner to Example
42.



[Table 13]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
221	OH		CH	Colorless powder	240-245 (Decomposed)	[DMSO-d ₆]: 2.24(s,3H), 2.44-2.54(m,4H), 3.25-3.36(m,4H), 4.89-5.10(m,4H), 5.81-5.92(m,1H), 6.24(d,J=6.0Hz,1H), 8.65(s,1H)	DMSO
222	OH		CH	Pale yellow powder	286-290 (Decomposed)		DMSO
224	OH		CF	Yellow powder	263 269 (Blackened)	[DMSO-d ₆]: 2.78-2.88(m,4H), 4.84-5.02(m,4H), 5.78-5.90(m,1H), 8.64(s,1H)	DMSO
225	OH		CF	Pale brown powder	234-238 (Decomposed)		DMSO

Example 44:

5-Hydroxy-1-(oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinolin-3-carboxylic acid (Compound No. 223)

220 mg of 60% sodium hydride was dispersed in 50 ml
5 of benzene, followed by the addition of 5.1 g of benzyl alcohol. They were then reacted. 1.7 g of Compound No. 23 was added, followed by a reaction at room temperature for 15 minutes. After the reaction mixture was washed twice with 250 ml portions of water, the reaction mixture was treated
10 with anhydrous magnesium sulfate and the solvent was distilled off. To the residue was added 40 ml of diisopropyl ether. A solid thus precipitated was collected by filtration. The solid and 260 mg of 10% palladium/carbon were added to a liquid mixture which consisted of 15 ml of
15 dichloromethane and 15 ml of methanol, followed by overnight hydrogenation. 50 ml of chloroform was added to dissolve the precipitate. The catalyst was filtered off and the filtrate was concentrated. Colorless powdery crystals thus precipitated were collected by filtration and then
20 washed with diisopropyl ether, whereby 790 mg of the title compound was obtained.

Melting point: 242-244°C (blackened).

$^1\text{H-NMR}$ (DMSO-d_6) δ :

4.87-5.05 (m, 4H), 5.78-5.91 (m, 1H), 8.78 (s, 1H).

Example 45:

Ethyl 5-amino-6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinolin-3-carboxylate (Compound No. 226)

60 g of methyl 2,3,4,6-tetrafluorobenzoate and 70 g of benzylamine were reacted under reflux for 1 hour in 400 ml of benzene. After the reaction mixture was allowed to cool down, it was washed successively with water, 1% hydrochloric acid and 1% aq. sodium carbonate, each in the amount of 600 ml. The reaction mixture was treated with anhydrous magnesium sulfate and then concentrated. Crystals thus precipitated were collected by filtration and thereafter washed with methanol. 30 g of the crystals and about 2 ml of palladium/carbon were added to a liquid mixture which consisted of 100 ml of acetic acid and 200 ml of methanol. The resultant mixture was hydrogenated for 1.5 hours. The catalyst was filtered off and the filtrate was concentrated, whereby methyl 6-amino-2,3,4-trifluorobenzoate was obtained as a crystalline residue.

The entire amount crystalline residue was added by portions to a liquid mixture which consisted of 200 ml of acetic acid containing 95 g of sodium perborate tetrahydrate suspended therein and 200 ml of trifluoroacetic acid and was stirred at 60°C. They were reacted at the same temperature for 1.5 hours. The solvent was concentrated to about 1/4 of the original volume. Subsequent to the addition of

1 l of water, extraction was conducted twice, each with 250 ml of chloroform. The chloroform layer was washed with water and then treated with anhydrous magnesium sulfate. The solvent was distilled off to obtain a crystalline residue, to which 50 ml of 10% sulfuric acid and 60 ml of acetic acid were added. The resulting mixture was stirred under reflux for 3 days. A majority of the acetic acid was distilled off. After the addition of 60 ml of water, the mixture thus obtained was extracted four times, each with 100 ml of chloroform. The chloroform layer was treated with anhydrous magnesium sulfate and then concentrated. A colorless powdery solid thus precipitated was dispersed in a liquid mixture of chloroform and n-hexane and then collected by filtration, whereby 5.7 g of 6-nitro-2,3,4-trifluorobenzoic acid was obtained.

After 9.3 g of the benzoic acid derivative was reacted with 4.5 ml of oxalyl chloride at 40°C for 1.5 hours in 70 ml of dichloromethane, excess reagents and solvent were distilled off. An acid chloride was thus obtained as an oily residue. Into a homogeneous solution which had been obtained by the reaction with 1.1 g of magnesium and 7.2 g of diethyl malonate in a liquid mixture consisting of 6 ml of ethanol and 50 ml of tetrahydrofuran at -60°C, a solution of the above acid chloride in 15 ml of tetrahydrofuran was added dropwise so that they were reacted. The temperature

of the reaction mixture was allowed to rise to room temperature, followed by the distillation of the solvents. To the residue were added 8.5 ml of concentrated hydrochloric acid, 50 ml of water and 100 ml of chloroform, followed by
5 separation into two layers. The chloroform layer was concentrated to obtain an oily residue. 2 g of p-toluenesulfonic acid monohydrate and 60 ml of water were added to the entire amount of the oily residue. They were reacted at about 100°C for 1.5 hours. The reaction mixture was allowed
10 to cool down, followed by the addition of 150 ml of dichloromethane. The resultant mixture was allowed to separate into two layers. The dichloromethane layer was washed with 1% aq. sodium hydrogencarbonate solution and was then treated with anhydrous magnesium sulfate. The dichloro-
15 methane solution was then concentrated, whereby ethyl 6-nitro-2,3,4-trifluorobenzoylacetate was obtained as an oily residue.

12.2 g of the ethyl benzoylacetate was heated to 140°C along with 12.2 g of acetic anhydride and 9.8 g of ethyl
20 orthoformate. They were reacted for 20 minutes. Excess reagents were distilled off at the same temperature under reduced pressure. The residue was allowed to cool down and then dissolved in 50 ml of dichloromethane. 3.1 g of 3-aminooxetane was added to the resultant solution. The mix-
25 ture was stirred at room temperature for 10 minutes, fol-

lowed by distillation of the solvent. To the residue were added 4.8 g of anhydrous potassium carbonate and 50 ml of dimethylformamide, followed by a reaction at 80°C for 25 minutes. To the reaction mixture were added 200 ml of
5 chloroform and 700 ml of water. The mixture thus formed was shaken. A solid thus precipitated was collected by filtration and then washed successively with water, methanol and chloroform, whereby 5.8 g of ethyl 6,7-difluoro-5-nitro-1-(oxetan-3-yl)-4-oxo-1,4-dihydroquinoline-4-carboxylate was
10 obtained as colorless needle crystals (m.p. 233-235°C).

2 g of the ethyl quinolonecarboxylate derivative and 0.2 g of 10% palladium/carbon were added to a liquid mixture which consisted of 100 ml of dichloromethane, 100 ml of methanol and 2 ml of acetic acid. The resultant mixture
15 was hydrogenated overnight. To the reaction mixture were added 100 ml of chloroform and 20 ml of methanol to dissolve a precipitate thus formed. The catalyst was filtered off. The filtrate was concentrated. Colorless needle crystals thus precipitated were collected by filtration and then
20 washed with chloroform, whereby 1.6 g of the title compound was obtained.

Melting point: 272-275°C (decomposed).

¹H-NMR (CDCl₃-CD₃OD, 10:1) δ:

1.40(t, J=7Hz, 3H), 4.38(q, J=7Hz, 2H), 4.95-5.02(m, 2H),
5.11-5.19(m, 2H), 5.35-5.48(m, 1H), 5.94(dd, J=12Hz, 6Hz,
1H), 8.42(s, 1H).

5 Example 46:

5-Amino-6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-
oxoquinoline-3-carboxylic acid (Compound No. 227)

To 20 ml of tetrahydrofuran, 110 mg of Compound No.
226 was added along with 1.5 g of a 10% aqueous solution of
10 tetra-n-butylammonium hydroxide. They were reacted at 60°C
for 10 minutes. To the reaction mixture was added 10 mg of
acetic acid and 3 ml of water and then concentrated. A
precipitate was collected by filtration and then successive-
ly washed with water, ethanol and diisopropyl ether, whereby
15 44 mg of the title compound was obtained as colorless pow-
dery crystals.

Melting point: ≥300°C.

¹H-NMR (DMSO-d₆) δ:

4.85-5.13(m, 4H), 5.60-5.71(m, 1H), 6.41(dd, J=12Hz, 6Hz,
20 1H), 7.95(br. 2H), 8.64(s, 1H).

Example 47:

5-Amino-6-fluoro-1-(oxetan-3-yl)-7-(piperazin-1-yl)-1,4-
dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.
228)

25 810 mg of Compound 226 and 810 mg of piperazine were

added to 5 g of dimethylsulfoxide and were reacted at about 100°C for 1 hour. The reaction mixture was cooled to about 80°C, followed by the addition of 325 mg of potassium hydroxide in 2 ml of water. They were reacted for 5 minutes, followed by the addition of 300 mg of acetic acid and 8 ml of ethanol. The resultant mixture was stirred at the same temperature and then allowed to cool down. A precipitate thus formed was collected by filtration and then washed with ethanol and diisopropyl ether. It was recrystallized from chloroform-methanol, whereby 610 mg of the title compound was obtained as pale yellow powdery crystals.

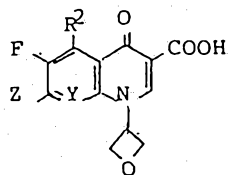
Melting point: 244-246°C.

¹H-NMR (DMSO-d₆) δ:

2.82-2.89(m,4H), 3.11-3.21(m,4H), 5.86-5.96(m,2H),
5.99-6.09(m,2H), 5.70-5.79(m,1H), 5.81(d,J=6Hz,1H),
7.37(br.s,2H), 8.50(s,1H).

Example 48:

Compound Nos. 229-232, which are shown in Table 14,
were obtained in a similar manner to Example 47.



[Table 14]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
229	-NH ₂		CH	Pale brown powder	241-244	[CDCl ₃ -CD ₃ OD, 10:1]: 2.39(s,3H), 2.58-2.68(m,4H), 3.25-3.33(m,4H), 5.00-5.19(m,4H), 5.47-5.56(m,1H), 5.66(d,J=6Hz,1H), 8.56(s,1H)	DMSO
230	-NH ₂		CH	Yellow powder	228-232	[DMSO-d ₆]: 1.03(d,J=6Hz,3H), 2.80-2.99(m,3H), 4.85-5.07(m,4H), 5.71-5.80(m,1H), 5.82(d,J=6Hz,1H), 7.34(brs,2H), 8.50(s,1H)	DMSO
231	-NH ₂		CH	Pale brown powder	268-271 (Blackened)	[DMSO-d ₆]: 1.63-1.75(m,1H), 1.93-2.06(m,1H)-3.71(m), 4.84-4.92(m,2H), 4.99-5.07(m,2H), 5.42(d,J=6Hz,1H), 7.20(brs,2H), 8.40(s,1H)	DMSO
232	-NH ₂		CH	Pale yellow powder	277-282 (Blackened)	[DMSO-d ₆]: 1.07(d,J=6Hz,3H), 2.39-2.54(m,1H)-3.89(m), 4.82-5.08(m,4H), 5.45(d,J=6Hz,1H), 5.60-5.71(m,1H), 7.27(brs,1H), 8.42(s,1H)	DMSO

Example 49:

Ethyl 1-(oxetan-3-yl)-5,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 233)

3 g of ethyl 2,3,4,6-tetrafluorobenzoylacetate, 3 g of acetic anhydride and 2.7 g of ethyl orthoformate were reacted at 140°C for 1.5 hours. At the same temperature, excess reagents were distilled out. The residue was allowed to cool down and then dissolved in 50 ml of dichloromethane. 0.6 g of 3-aminooxetane was added, followed by concentration. 5 ml of diisopropyl ether was added. The resultant mixture was left over. Crystals thus precipitated were collected by filtration. Those crystals were added to 40 ml of tetrahydrofuran, followed by the addition of 280 mg of 60% sodium hydride under stirring and reflux. They were reacted for 10 minutes. After the solvent was distilled off, 100 ml of chloroform and 20 ml of water were added. The resulting mixture was shaken and then allowed to separate into two layers. The chloroform layer was treated with anhydrous magnesium sulfate and concentrated. Colorless crystals thus precipitated were collected by filtration and then washed with diisopropyl ether, whereby 1.97 g of the title compound was obtained.

Melting point: 169-171°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.40(t, J=7Hz, 3H), 4.39(q, J=7Hz, 2H), 4.93-5.04(m, 2H),
5.08-5.19(m, 2H), 5.73-5.84(m, 1H), 6.96(dt, J=6Hz,
J=11Hz, 1H), 8.53(s, 1H).

5 Example 50:

1-(Oxetan-3-yl)-5,7,8-trifluoro-1,4-dihydro-4-oxo-
quinoline-3-carboxylic acid (Compound No. 234)

650 mg of Compound No. 233, 1.2 ml of 2N aq. sodium
hydroxide solution and 50 mg of benzyltriethylammonium
10 chloride were added to 20 ml of tetrahydrofuran. The
resultant mixture was stirred under reflux for 2.5 hours. A
majority of the tetrahydrofuran was distilled off, followed
by the addition of 5 ml of ethanol. The resulting mixture
was refluxed for 5 minutes and then allowed to cool down,
15 whereby 560 mg of the title compound was obtained as pale
brownish yellow powder.

Melting point: $>300^\circ\text{C}$.

$^1\text{H-NMR}$ (DMSO-d_6) δ :

4.79-5.03(m, 4H), 5.67-5.80(m, 1H), 7.40(dt, J=6Hz, 11Hz,
20 1H), 8.55(s, 1H).

Example 51:

5,8-Difluoro-1-(oxetan-3-yl)-7-(piperazin-1-yl)-1,4-
dihydro-4-oxoquinoline-3-carboxylic acid (Compound No.
235)

25 100 mg of Compound No. 234, 100 mg of piperazine and

400 mg of dimethylsulfoxide were stirred at about 100°C for 20 minutes. To the resultant mixture was added 1 ml of ethanol and then refluxed for 2 minutes. The reaction mixture was allowed to cool down. Pale yellow powdery crystals thus precipitated were collected by filtration and then washed successively with ethanol and chloroform, whereby 60 mg of the title compound was obtained.

Melting point: >300°C.

¹H-NMR (DMSO-d₆) δ:

10 2.76-2.90(m,4H), 3.14-3.25(m,4H), 4.81-5.05(m,4H),
 5.76-5.89(m,1H), 7.12(dd,J=7Hz,14Hz,1H), 8.64(s,1H).

Example 52:

Ethyl 8-chloro-6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 236)

15 7 g of ethyl 2,3-dichloro-4,5-difluoro-benzoylacetate,
7.5 g of acetic anhydride and 6 g of ethyl orthoformate were reacted at 140°C for 40 minutes. Excess reagents were distilled off at the same temperature under reduced pressure and the residue was allowed to cool down. The residue was
20 dissolved in 40 ml of dichloromethane, followed by the addition of 1.8 g of 3-aminooxetane. The mixture thus obtained was concentrated. A precipitate was dispersed in chloroform-diisopropyl ether and then collected by filtration. The precipitate was dissolved in 70 ml of tetra-
25 hydrofuran, followed by the addition of 640 mg of 60% sodium

hydride. The resultant mixture was stirred at 60°C for 30 minutes. The solvent was distilled off and 150 ml of chloroform and 50 ml of water were added to the residue.

The mixture thus obtained was shaken and then allowed to
5 separate into two layers. The chloroform layer was treated with anhydrous magnesium sulfate and then concentrated. Colorless powdery crystals thus precipitated were dispersed in chloroform-diisopropyl ether and then collected by filtration, whereby 3.5 g of the title compound was obtained.

10 Melting point: 139-141°C.

¹H-NMR (CDCl₃) δ:

1.42 (t, J=7Hz, 3H), 4.42 (q, J=7Hz, 2H), 4.82-4.91 (m, 2H),
5.14-5.24 (m, 2H), 6.01-6.10 (m, 1H), 8.24 (dd, J=10Hz, 8Hz, -
1H), 8.90 (s, 1H).

15 Example 53:

8-Chloro-6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 237)

To 16 ml of tetrahydrofuran, 900 mg of Compound No. 236 was added along with 1.5 ml of 2N aq. sodium hydroxide
20 solution. They were reacted at 60°C for 40 minutes. To the reaction mixture was added 200 mg of acetic acid. The resultant mixture was stirred for 10 minutes and then allowed to cool down. A reaction product precipitated in the form of pale yellow powder was collected by filtration and
25 then washed successively with ethanol and diisopropyl ether,

whereby 650 mg of the title compound was obtained.

Melting point: >300°C.

$^1\text{H-NMR}$ ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 10:1) δ :

4.84-5.93 (m, 2H), 5.12-5.23 (m, 2H), 6.07-6.18 (m, 1H),
5 8.21 (dd, $J=10\text{Hz}, 8\text{Hz}$, 1H), 9.08 (s, 1H).

Example 54:

8-Chloro-6-fluoro-7-(4-methylpiperazin-1-yl)-1-(oxetan-
3-yl)-1,4-dihydro-4-oxoquinolin-3-carboxylic acid
(Compound No. 238)

10 100 mg of Compound No. 237, 100 mg of N-methyl-
piperazine and 300 mg of dimethylsulfoxide were reacted at
about 100°C for 15 minutes. The reaction mixture was al-
lowed to cool down and 4 ml of diisopropyl ether was added.
The resulting mixture was shaken and the upper layer was
15 decanted with an oily precipitate left behind. To the oily
precipitate was added 0.5 ml of ethanol. Colorless prism
crystals thus formed were collected by filtration and then
washed successively with ethanol and diisopropyl ether,
whereby 85 mg of the title compound was obtained.

20 Melting point: 211-212°C.

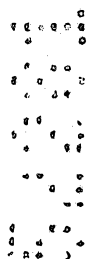
$^1\text{H-NMR}$ (DMSO-d_6) δ :

2.25 (s, 3H), 2.40-2.54 (m, 4H), 4.72-4.82 (m, 2H),
5.04-5.15 (m, 2H), 6.04-6.15 (m, 1H), 7.95 (d, $J=12\text{Hz}$, 1H),
8.98 (s, 1H).

Example 55

Compound Nos. 239 and 240, which are shown in Table 15, were obtained in a similar manner to Example 54.

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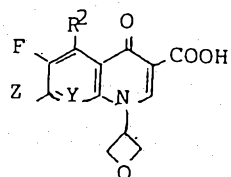


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[Table 15]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
239	H		CCl	Colorless powder	230-233 (Decomposed)	[DMSO-d ₆]: 2.80-2.89(m,4H), 3.22-3.31(m,4H) 4.70-4.80(m,2H), 5.03-5.12(m,2H), 6.01-6.10(m,1H), 7.92(d,J=10Hz,1H), 8.95(s,1H)	DMSO
240	H		CCl	Pale brown powder	168-175 (Decomposed)	[DMSO-d ₆]: 1.63-1.75(m,1H), 1.97-2.09(m,1H)-3.88(m), 4.70-4.80(m,2H), 5.04-5.14(m,2H), 5.96-6.07(m,1H), 8.82(d,J=10Hz,1H), 8.87(s,1H)	DMSO

Example 56

Ethyl 6,7-difluoro-1-(oxetan-3-yl)-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (Compound No. 241)

2.1 g of ethyl 2-chloro-3-methyl-4,5-difluorobenzoyl-
5 acetate, 2.0 ml of ethyl orthoformate and 3.4 ml of acetic
anhydride were reacted at 130°C for 4 hours. Volatile com-
ponents were distilled off under reduced pressure, followed
by the addition of 20 ml of benzene. To the resultant mix-
ture was added at room temperature 0.6 g of 3-aminooxetane.
10 They were reacted at the same temperature for 15 hours. The
solvent was distilled off, followed by the addition of
hexane. A solid thus formed was collected by filtration
(yield: about 2.3 g).

In 8 ml of dimethylformamide, 0.8 g of the solid and
15 0.32 g of potassium carbonate were reacted at 110°C for 20
hours. The solvent was distilled off. The residue was ex-
tracted with 20 ml of chloroform. After the chloroform
solution was washed with water and then dried over $MgSO_4$,
the solvent was distilled off. Hexane was added. A solid
20 thus formed was collected by filtration, whereby 0.44 g of
the title compound was obtained as a yellow solid.
Melting point: 157-165°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.42 (t, $J=7.1\text{Hz}$, 3H), 2.41 (d, $J=2.9\text{Hz}$, 3H),
4.42 (q, $J=7.1\text{Hz}$, 2H), 4.90-5.20 (m, 4H), 5.61 (m, 1H),
8.08 (d, $J=9.3\text{Hz}$, 1H), 9.07 (s, 1H).

5 Example 57:

6,7-Difluoro-1-(oxetan-3-yl)-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (Compound No. 242)

0.44 g of Compound No. 241 was dissolved in 10 ml of tetrahydrofuran, to which 1 ml of 2N aq. sodium hydroxide solution was added. They were reacted under reflux for 5 hours. After the organic solvent was distilled off, the residue was rendered acidic with 1N HCl. A solid thus formed was collected by filtration. The solid was washed successively with water, ethanol and ether, each in the amount of 1 ml, whereby 0.20 g of the title compound was obtained as a pale brown solid.

Melting point: 193-202°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

2.50 (d, 3H), 4.92-5.23 (m, 4H), 5.77 (m, 1H),
8.17 (d, $J=9.16\text{Hz}$, 1H), 9.32 (s, 1H).

Example 58

7-(3-Aminopyrrolidin-1-yl)-6-fluoro-1-(oxetan-3-yl)-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid
(Compound No. 243)

25 In 1 ml of DMSO, 100 mg of Compound No. 242 and 85 mg

of 3-aminopyrrolidine were reacted at 80°C for 2 hours. The reaction mixture was washed three times with diisopropyl ether. The residue was solidified with ether and the resultant solid was collected by filtration. The solid was
5 then washed successively with chloroform, ethanol and hexane, each in the amount of 3 ml, whereby 38 mg of the title compound was obtained as a brown solid.

Melting point: $\geq 230^{\circ}\text{C}$ (carbonized)

Example 59

10 Ethyl 5-dimethylamino-6,7,8-trifluoro-1-(oxetan-3-yl)-
1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound
No. 244)

In 18 ml of toluene, 800 mg of Compound No. 23, 4.6 g
of triethylamine and 1.88 g of dimethylamine hydrochloride
15 were stirred at room temperature for 2 hours. After the
solvent was distilled off, the residue was subjected to
column chromatography on silica gel (chloroform/acetone =
10/1), whereby 790 mg of the title compound was obtained as
a yellow solid.

20 Melting point: $130-134^{\circ}\text{C}$.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.38(t, $J=7\text{Hz}$, 3H), 2.98(s, 3H), 2.99(s, 3H), 4.38(q, 7Hz,
2H), 4.9-5.0(m, 2H), 5.05-5.15(m, 2H), 5.55-5.7(m, 1H),
8.41(s, 1H).

Example 60:

5-Dimethylamino-6,7,8-trifluoro-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 245)

5 790 mg of Compound No. 244 was dissolved in 15 ml of tetrahydrofuran. Under reflux, 2.5 ml of 1N aq. sodium hydroxide solution was added dropwise. Then, they were then reacted for 30 minutes. After the organic solvent was distilled off, the residue was rendered acidic (about pH 5.0)
10 with 20% acetic acid. A solid thus formed was collected by filtration. The solid was washed successively with water (5 ml x 2), methanol (3 ml) and ether (5 ml x 2), whereby 433 mg of the title compound was obtained as a yellow solid. Melting point: 173-175°C.

15 ¹H-NMR (CDCl₃) δ:

3.05(s,3H), 3.06(s,3H), 4.86-5.2(m,4H), 5.65-5.8
(m,1H), 8.69(s,1H).

Example 61:

20 5-Dimethylamino-6,8-difluoro-7-(4-methylpiperazin-1-yl)-1-(oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound No. 246)

In 1 ml of dimethylsulfoxide, 100 mg of Compound No. 245 and 100 mg of 1-methylpiperazine were reacted at 80°C for 1.5 hours. To the reaction mixture was added 150 ml of
25 ether, followed by stirring. After decantation, the residue

was solidified with ethanol and ether, each in the amount of 10 ml. A solid thus formed was collected by filtration, whereby 55 mg of the title compound was obtained as a yellow powder.

5 Melting point: 186-187°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

2.36(s,3H), 2.54(s,4H), 2.99(s,3H), 3.00(s,3H),
3.37(s,4H), 4.85-4.95(m,2H), 5.0-5.1(m,2H), 5.6-
5.75(m,1H), 8.59(s,1H).

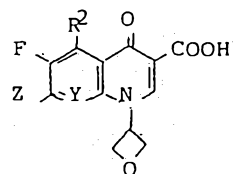
10 Example 62

Compound Nos. 247 and 248, which are shown in Table 16, were obtained in a similar manner to Example 61.

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[Table 16]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
247	Me-N-Me		CF	Yellow powder solid	150-154	[CDCl ₃ + DMSO-d ₆]: 1.65-1.9(m,1H), 2.0-2.25(m,1H), 2.97(s,3H), 2.98(s,3H), 3.3-3.4(m,1H), 3.55-4.0(m,4H), 4.8-5.1(m,4H), 5.55-5.71(m,1H), 8.55(s,1H)	DMSO
248	Me-N-Me		CF	Yellow powder solid	150-159	[CDCl ₃ + DMSO-d ₆]: 2.99(s,3H), 3.00(s,3H), 2.8-3.1(br,4H), 3.37(s,4H), 4.8-5.15(m,4H), 5.6-5.8(m,1H), 8.63(s,1H)	DMSO

Example 63

Ethyl 6,7,8-trifluoro-1-(thietan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 249)

- 1.32 g of ethyl 2,3,4,5-tetrafluorobenzoylacetate, 5 1.25 ml of ethyl orthoformate and 2.13 ml of acetic anhydride were reacted at 130°C for 1 hour. Volatile components were distilled off under reduced pressure. The residue was added with 30 ml of benzene and also with a solution of 623 mg of 3-aminothietane in 5 ml of ethanol.
- 10 The resultant mixture was stirred at room temperature for 12 hours. The solvent was distilled off and hexane was added to the residue. A solid thus formed was collected by filtration, whereby 1.16 g of a white solid was obtained. In 5 ml of dimethylformamide, 1.16 g of the white solid and 440
- 15 mg of potassium carbonate were reacted at 100°C for 30 minutes. The solvent was distilled off, followed by extraction with 50 ml of chloroform. The organic layer was washed with 10 ml of water and then dried over anhydrous sodium sulfate. The solvent was distilled off. Ether was
- 20 added to the residue. A solid thus formed was collected by filtration, whereby 785 mg of the title compound was obtained as a pale yellow solid.

Melting point: 160-164°C.

¹H-NMR (CDCl₃) δ:

1.43 (t, J=7Hz, 3H), 3.45-3.65 (m, 2H), 3.8-4.0 (m, 2H),
4.42 (q, J=7Hz, 2H), 6.0-6.2 (m, 1H), 8.08-8.13 (m, 1H),
8.86 (s, 1H).

5 Example 64:

6,7,8-Trifluoro-1-(thietan-3-yl)-1,4-dihydro-4-
oxoquinoline-3-carboxylic acid (Compound No. 250)

750 mg of Compound No. 249 was dissolved in 5 ml of
tetrahydrofuran and under reflux, 3 ml of 2N aq. sodium
10 hydroxide solution was added dropwise. They were reacted
for 10 minutes. The solvent was distilled off and the
residue was acidified to pH 5-4 with 20% acetic acid. A
solid thus formed was collected by filtration. The solid
was washed successively with water (3 ml x 2), ethanol (5
15 ml x 2) and ether (5 ml x 2), whereby 690 mg of the title
compound was obtained as a slightly red solid.

Melting point: 172-175°C.

¹H-NMR (CDCl₃) δ:

3.5-3.63 (m, 2H), 3.8-4.0 (m, 2H), 6.1-6.3 (m, 1H), 8.1-
20 8.15 (m, 1H), 9.09 (s, 1H).

Example 65

6,8-Difluoro-7-(4-methylpiperazin-1-yl)-1-(thietan-3-
yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid
(Compound No. 251)

25 In 1 ml of dimethylformamide, 60 mg of Compound No.

250 and 100 mg of 1-methylpiperazine were reacted at 80°C for 40 minutes. The solvent was distilled off. To the residue was added 4 ml of ethanol, so that the residue was solidified. The solid thus obtained was ground and collected by filtration, whereby 41 mg of the title compound was obtained as pale yellow powder.

Melting point: 204-206°C.

¹H-NMR (CDCl₃) δ:

2.38(s,3H), 2.58(s,4H), 3.44(s,4H), 3.5-3.65(m,2H),
3.85-4.0(m,2H), 6.05-6.15(m,1H), 7.94(d,J=11.7Hz,1H),
8.99(s,1H).

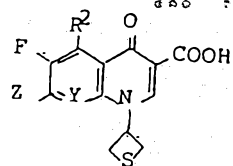
Example 66

Compound Nos. 252-256, which are shown in Table 17, were obtained in a similar manner to Example 65.

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[Table 17]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
252	H		CF	Colorless powder	210-213	[CDCl ₃]: 3.41(s,4H), 3.45-3.6(m,2H), 3.85(s,4H), 3.8-4.0(m,2H), 6.0-6.2(m,1H), 7.96(d,J=11.7Hz,1H), 8.99(s,1H)	DMF
253	H		CF	Colorless powder	215-217	[CDCl ₃]: 2.81(s,4H), 3.4-3.6(m,2H), 3.61(s,4H), 3.85-4.0(m,2H), 6.05-6.2(m,1H), 7.97(d,J=11.5Hz,1H), 9.01(s,1H)	DMF
254	H		CF	Yellow powder	215-222	[DMSO-d ₆]: 1.6-1.75(m,1H), 1.9-2.05(m,1H), 3.8-4.0(m,2H), 5.9-6.1(m,1H), 7.69(d,J=13.7Hz,1H), 8.78(s,1H)	DMSO
255	H		CF	Yellow powder	283-287	[DMSO-d ₆]: 1.8-2.05(m,2H), 3.3-3.5(m,4H), 3.6-3.8(m,1H), 3.8-4.05(m,4H), 4.38(brs,1H), 5.07(s,1H), 5.9-6.1(m,1H), 7.73(d,J=14.2Hz,1H), 8.82(s,1H)	DMSO + Et ₃ N
256	H		CF	Colorless powder	210-212	[DMSO-d ₆ + CF ₃ EtOH]: 1.21(t,J=7.3Hz,3H), 1.6-1.8(m,1H), 2.05-2.2(m,1H), 2.8-3.1(m,4H), 3.4-3.6(m,3H), 3.7-3.9(m,3H), 3.95-4.1(m,2H), 5.85-6.05(m,1H), 7.75(d,J=14.2Hz,1H), 8.47(brs,2H), 8.83(s,1H)	DMSO + Et ₃ N

Referential Example

Synthesis of 3-aminothietane:

(1) 3-Phthalimidoylthietane:

14.3 g of 3-hydroxythietane, 418 g of triphenyl-
5 phosphine and 23.4 g of phthalimide were dissolved in 200
ml of tetrahydrofuran, followed by the dropwise addition of
a solution of 27.8 g of diethyl azodicarboxylate in 70 ml
of tetrahydrofuran at room temperature over 1 hour. They
were reacted for further 12 hours and the solvent was then
10 distilled off. The residue was subjected to columnchromato-
graphy on silica gel (chloroform/ethyl acetate = 50:1).
Relevant fractions were collected, from which the solvents
were distilled off. To the residue was added 300 ml of
isopropyl ether. A solid thus formed was collected by fil-
15 tration, whereby 9.6 g of the title compound was obtained as
a slightly yellow solid.

Melting point: 118-126°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

3.15-3.25(m, 2H), 4.25-4.4(m, 2H), 5.5-5.7(m, 1H), 7.65-
20 7.95(m, 4H).

(2) 3-Aminothietane:

In 30 ml of methanol, 1.53 g of 3-phthalimidoyl-
thietane and 0.29 ml of hydrazine anhydride were reacted
for 1 hour under reflux. After the reaction mixture was al-
25 lowed to cool down, 40 ml of ether was added. Insoluble

matter was filtered off. The filtrate was distilled under normal pressure. The residue was provided, as was, for subsequent reactions.

Example 67

- 5 Ethyl 1-(1-diphenylmethylazetidin-3-yl)-6,7-difluoro-1,4-dihydro-4-oxoquinolin-3-carboxylate (Compound No. 257)

4.92 g of ethyl 2,4,5-trifluorobenzoylacetate, 5 ml of ethyl orthoformate and 8.5 ml of acetic anhydride were
10 reacted at 130°C for 1.5 hours. After volatile components were distilled off, 50 ml of benzene and 4.77 g of 3-amino-1-diphenylmethylazetidine were added. They were reacted at room temperature for 30 minutes. The solvent was distilled off and 25 ml of dimethylformamide and 2.8 g of potassium
15 carbonate were added to the residue. They were reacted at 140°C for 20 minutes. The solvent was distilled off and 50 ml of hexane was added to the residue. A solid thus formed was collected by filtration and then washed with water (10 ml x 2). The solid was dissolved in 50 ml of
20 chloroform. The resultant solution was dried over anhydrous sodium sulfate. The solvent was distilled off, followed by the addition of ether. A solid thus formed was collected by filtration, whereby 9 g of the title compound was obtained as a pale orange solid.

25 Melting point: 196-201°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.35(t, $J=7\text{Hz}$, 3H), 3.3-3.5(m, 2H), 3.85-3.95(m, 2H),
4.4(q, $J=7\text{Hz}$, 2H), 4.42(s, 1H), 4.85-5.0(m, 1H), 7.05-
7.15(m, 1H), 7.2-7.5(m, 10H), 8.2-8.35(m, 1H),
5 8.61(s, 1H).

Example 68

1-(1-Diphenylmethylazetidin-3-yl)-6,7-difluoro-1,4-
dihydro-4-oxoquinoline-3-carboxylic acid (Compound
No. 258)

10 5.0 g of Compound No. 257 was dissolved in 120 ml of
tetrahydrofuran and under reflux, 9.8 ml of 2N aq. sodium
hydroxide solution and 13.7 ml of water were added drop-
wise. They were reacted for 45 minutes. After the reaction
mixture was allowed to cool down, the solvent was distilled
15 off and the residue was acidified to pH 4-5 with 20% acetic
acid. A solid thus formed was collected by filtration. The
solid was washed successively with 3 ml of water, ethanol
(5 ml x 3) and ether (10 ml), whereby 4.06 g of the title
compound was obtained as a pale yellow solid.

20 Melting point: 245-247°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

3.3-3.5(m, 2H), 4.85-5.0(m, 2H), 4.43(s, 1H), 5.0-
5.1(m, 1H), 7.2-7.55(m, 11H), 8.25-8.35(m, 1H),
8.85(s, 1H).

Example 69

1-(Azetidin-3-yl)-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (Compound No. 259)

5 1.0 g of Compound No. 258 was dissolved in 100 ml of tetrahydrofuran, followed by the addition of 0.54 ml of 4N-HCl/dioxane under ice cooling. The resultant mixture was stirred for 30 minutes. The solvent was distilled off and 30 ml of ether was added. 1.01 g of a solid was collected
10 by filtration. 200 mg of the solid was dissolved in 80 ml of methanol, followed by the addition of 40 mg of palladium black. The thus-prepared mixture was stirred at room temperature for 1 day under hydrogen gas. The catalyst was filtered off and the filtrate was concentrated under reduced
15 pressure. To the residue was added 10 ml of ether. A solid thus formed was collected by filtration, whereby 100 mg of the title compound was obtained as slightly yellow solid.

Melting point: $\geq 250^{\circ}\text{C}$ (colored and decomposed).

20 $^1\text{H-NMR}$ (DMSO-d_6) δ :

4.5-4.7(m, 4H), 5.65-5.8(m, 1H), 8.0-8.1(dd, $J=12.5\text{Hz}$, $J=6.2\text{Hz}$, 1H), 8.29-8.36(dd, $J=10.3\text{Hz}$, $J=8.8\text{Hz}$, 1H), 9.0(s, 1H).

Example 70

1-(Azetidin-3-yl)-6-fluoro-7-(4-methylpiperazin-1-yl)-
1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound
No. 260)

5 In 500 mg of dimethylformamide, 60 mg of Compound No.
259 and 80 mg of 1-methylpiperazine were reacted at 80°C for
1 hour. After the solvent was distilled off, 5 ml of
ethanol was added to the residue to solidify the latter.
The resulting solid was collected by filtration and then
10 washed successively with ethanol (5 ml) and ether (5 ml),
whereby 50 mg of the title compound was obtained as a pale
yellow solid.

Melting point: $\geq 220^{\circ}\text{C}$ (decomposed).

$^1\text{H-NMR}$ (DMSO-d_6) δ :

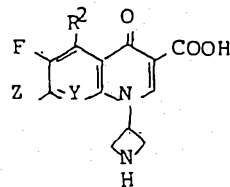
15 2.2(s,3H), 2.5(brs,4H), 4.0-4.2(m,4H), 5.5-5.7(m,1H),
7.00(d,J=6.8Hz,1H), 7.94(d,J=13.8Hz,1H), 8.8(s,1H).

Example 71

Compound Nos. 261-263, which are shown in Table 18,
were obtained in a similar manner to Example 70.

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[Table 18]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
261	H		CH	Yellow powder	Carbonized (210 °C and up)	[DMSO-d ₆]: 3.12(brs, 4H), 3.42(brs, 4H), 3.9-4.2(m, 4H) 5.6-5.7(m, 1H), 7.03-7.10(d, 1H), 7.93-7.98 (d, J=12.7Hz, 1H), 8.8(s, 1H)	CHCl ₃ + Et ₃ N
262	H		CH	Pale brown powder	Carbonized (230 °C and up)		CHCl ₃ + Et ₃ N
263	H		CH	Pale yellow powder	Carbonized (245 °C and up)		CHCl ₃ + Et ₃ N

Example 72:

Ethyl 6,7-difluoro-1-(thietan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Compound No. 264)

2.46 g of ethyl 2,4,5-trifluorobenzoylacetate, 2.5 ml
5 of ethyl orthoformate and 4.2 ml of acetic anhydride were
reacted at 130°C for 3 hours. Volatile components were dis-
tilled off under reduced pressure. To the residue were
added 40 ml of benzene and a solution of 1.3 g of 3-
aminothietane in 20 ml of methanol. The resultant mixture
10 was stirred at room temperature for 12 hours. The solvent
was distilled off and 20 ml of hexane was added to the
residue. A solid thus formed was collected by filtration,
whereby 2.5 g of a pale yellow solid was obtained. In 10
ml of dimethylformamide, 2.5 g of the solid and 1 g of
15 potassium carbonate were stirred at 100°C for 30 minutes.
The solvent was distilled off and the residue was extracted
with 100 ml of chloroform. The extract was washed with
20 ml of water. The organic layer was dried over anhydrous
sodium sulfate and the solvent was then distilled off. The
20 residue was subjected to column chromatography on silica gel
(chloroform/ethyl acetate = 8:1). Relevant fractions were
collected, followed by distillation of the solvents. To the
residue was added 30 ml of ether. A solid thus formed was
collected by filtration, whereby 1.29 g of the title com-
25 pound was obtained as a colorless solid.

Melting point: 174-177°C.

$^1\text{H-NMR}$ (CDCl_3) δ :

1.43 (t, $J=7\text{Hz}$, 3H), 3.54-3.60 (dd, $J=9.77\text{Hz}$, $J=8.33\text{Hz}$, 2H),
3.90-3.97 (dd, $J=9.77\text{Hz}$, $J=9.27\text{Hz}$, 2H), 4.42 (q, $J=7\text{Hz}$, 2H),
5 5.57-5.75 (m, 1H), 7.41-7.48 (dd, $J=11.23\text{Hz}$, $J=5.86\text{Hz}$, 1H),
8.27-8.35 (dd, $J=10.25\text{Hz}$, $J=8.79\text{Hz}$, 1H), 8.70 (s, 1H).

Example 73:

6,7-Difluoro-1-(thietan-3-yl)-1,4-dihydro-4-oxo-
quinoline-3-carboxylic acid (Compound No. 265)

10 1.24 g of Compound No. 264 was dissolved in 30 ml of
tetrahydrofuran, followed by the addition of 1N aq. sodium
hydroxide solution. Under reflux, they were reacted for 20
minutes. The solvent was distilled off under reduced pres-
sure and the residue was neutralized with 20% acetic acid.
15 A solid thus formed was collected by filtration and then
washed successively with water (2 ml), ethanol (5 ml x 3)
and ether (5 ml x 2), whereby 970 mg of the title compound
was obtained as a pale yellow solid.

Melting point: 251-256°C.

20 $^1\text{H-NMR}$ (CDCl_3 + DMSO-d_6) δ :

3.60-3.68 (dd, $J=8.3\text{Hz}$, $J=9.76\text{Hz}$, 2H), 3.97 (t, $J=9.28\text{Hz}$,
2H), 5.85-6.05 (m, 1H), 7.84-7.91 (dd, $J=11.23\text{Hz}$, $J=6.35\text{Hz}$,
1H), 8.29-8.36 (dd, $J=8.79\text{Hz}$, $J=9.77\text{Hz}$, 1H), 9.02 (s, 1H).

Example 74

6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(thietan-3-yl)-
1,4-dihydro-4-oxoquinoline-3-carboxylic acid (Compound
No. 266)

5 In 0.5 ml of dimethylsulfoxide, 100 mg of Compound
No. 265 and 100 mg of 1-methylpiperazine were reacted at
80°C for 1 hour. The reaction mixture was allowed to cool
down, to which 20 ml of ether was added. A solid thus
formed was collected by filtration. The solid was washed
10 successively with ethanol (3 ml x 3) and ether (3 ml x 3),
whereby 42 mg of the title compound was obtained as pale
yellow powder.

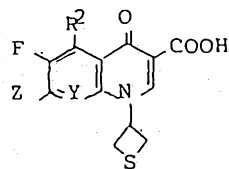
Melting point: 231-237°C.

¹H-NMR (CDCl₃) δ:

15 2.39(s, 3H), 2.65(t, J=4.88Hz, 4H), 3.38(t, J=4.88Hz, 4H),
3.56-3.63(dd, J=8.3Hz, J=9.77Hz, 2H), 3.96-4.03(dd,
J=9.28Hz, J=9.76Hz, 2H), 5.7-5.9(m, 1H), 7.04(d, J=6.84Hz,
1H), 8.06(d, J=13.19Hz, 1H), 8.82(s, 1H).

Example 75

20 Compound Nos. 267-272, which are shown in Table 19,
were obtained in a similar manner to Example 74.



[Table 19]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
267	H		CH	Pale yellow powder	216-223	[DMSO-d ₆]: 2.91(bris,4H), 3.2(bris,4H), 3.6-3.67(m,2H), 3.97-4.05(m,2H), 6.1-6.35(m,1H), 7.34(d,J=7.33Hz,1H), 7.92(d,J=14.16Hz,1H), 8.81(s,1H)	DMSO
268	H		CH	Colorless powder	292-296	[DMSO-d ₆]: 3.35(bris,4H), 3.55-3.7(m,2H), 3.80(bris,4H), 3.9-4.1(m,2H), 6.1-6.25(m,1H), 7.37(d,J=7.32Hz,1H), 7.95(d,J=13.67Hz,1H), 8.81(s,1H)	DMSO
269	H		CH	Colorless powder	290-295	[DMSO-d ₆]: 2.81(bris,4H), 3.63(bris,4H), 3.4-3.65(m,2H), 3.9-4.1(m,2H), 6.1-6.3(m,1H), 7.42(d,J=6.84Hz,1H), 7.94(d,J=13.2Hz,1H), 8.82(s,1H)	DMSO
270	H		CH	Pale yellow powder	270-274	[DMSO-d ₆]: 1.65-1.8(m,1H), 1.95-2.1(m,1H), 3.4-3.75(m,6H), 3.9-4.05(m,2H), 6.02-6.18(m,1H), 6.84(d,J=7.82Hz,1H), 7.81(d,J=14.65Hz,1H), 8.69(s,1H)	DMSO
271	H	 Trans(-)-form	CH	Pale yellow powder	180-186	[DMSO-d ₆]: 1.12(d,J=6.35Hz,3H), 2.4-2.6(m,1H), 3.5-3.88(m,4H), 3.9-4.15(m,2H), 6.05-6.25(m,1H), 6.89(d,J=7Hz,1H), 7.87(d,J=14.16Hz,1H), 8.72(s,1H)	DMSO + Et ₃ N
272	H		CH	Colorless powder	268-273	[DMSO-d ₆]: 1.23(t,J=7.3Hz,3H), 1.75-1.9(m,1H), 2.15-2.3(m,1H), 2.6-2.86(m,1H), 2.9-3.15(m,4H), 3.45-3.9(m,6H), 3.95-4.1(m,2H), 6.0-6.15(m,1H), 6.85(d,J=6.84Hz,1H), 7.85(d,J=14.16Hz,1H), 8.71(s,1H)	DMSO + Et ₃ N

Example 76

Ethyl 7-chloro-6-fluoro-1-(thietan-3-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Compound No. 273)

2.8 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate,
5 2.5 ml of ethyl orthoformate and 4.2 ml of acetic anhydride
were reacted at 130°C for 3 hours. Volatile components were
distilled off under reduced pressure. To the residue was
added 40 ml of benzene and a solution of 1.3 g of 3-
aminothietane in 20 ml of methanol. The resultant mixture
10 was stirred at room temperature for 12 hours. The solvent
was distilled off and to the residue was added 20 ml of
hexane. A solid thus formed was collected by filtration,
whereby 3.02 g of a colorless solid was obtained. 2.95 g of
the solid was dissolved in 40 ml of tetrahydrofuran, to
15 which 430 mg of sodium hydride (content: 60%) was added un-
der ice cooling. The resultant mixture was stirred at the
same temperature for 30 minutes and then under reflux for
further 4 hours. The solvent was distilled off and 20 ml
of water was added to the residue. The resultant mixture
20 was extracted with 100 ml of chloroform. The organic layer
was dried over anhydrous sodium sulfate and the solvent was
distilled off. The residue was subjected to
column chromatography on silica gel (chloroform/ethyl acetate
= 8:1). Relevant fractions were collected. The solvents
25 was distilled off. To the residue was added 30 ml of

ether. A solid thus formed was collected by filtration, whereby 1.11 g of the title compound was obtained as a colorless solid.

Melting point: 157-161°C.

5 $^1\text{H-NMR}$ (CDCl_3) δ :

1.43 (t, $J=7.2\text{Hz}$, 3H), 3.54-3.62 (dd, $J=8.3\text{Hz}$, $J=9.76\text{Hz}$, 2H),
3.86-3.94 (dd, $J=9.28\text{Hz}$, $J=9.76\text{Hz}$, 2H), 4.43 (q, $J=7.2\text{Hz}$,
2H), 6.35-6.55 (m, 1H), 8.45 (d, $J=7.33\text{Hz}$, 1H), 8.87 (s, 1H).

Example 77

10 6-Fluoro-7-(4-methylpiperazin-1-yl)-1-(thietan-3-yl)-
1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid
(Compound No. 274)

In 10 ml of chloroform, 100 mg of Compound No. 273
and 100 mg of 1-methylpiperazine were reacted for 3 hours
15 under reflux. After the reaction mixture was allowed to
cool down, the solvent was distilled off under reduced pres-
sure. To the residue was added 5 ml of ethanol and 2 ml of
10% aq. sodium carbonate solution. The resultant mixture
was stirred under reflux for 4 hours. After the reaction
20 mixture was allowed to cool down, the solvent was distilled
off under reduced pressure. The residue was neutralized
with 20% acetic acid. A solid thus formed was collected by
filtration and then washed successively with ethanol (3 ml
x 2) and ether (3 ml x 2), whereby 82 mg of the title com-
25 pound was obtained as pale yellow powder.

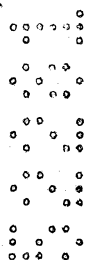
Melting point: 270-280°C.

^1H -NMR (DMSO- d_6) δ :

2.57(s, 3H), 3.03(brs, 4H), 3.35-3.55(m, 2H),
3.9-4.2 (br, 4H), 4.21(brs, 2H), 6.1-6.25(m, 1H),
5 8.18(d, $J=14.16\text{Hz}$, 1H), 8.87(s, 1H).

Example 78

Compound Nos. 275-281, which are shown in Table 20,
were obtained in a similar manner to Example 77.



10

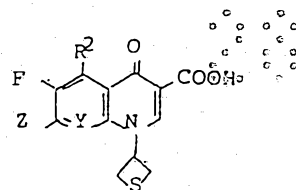


15



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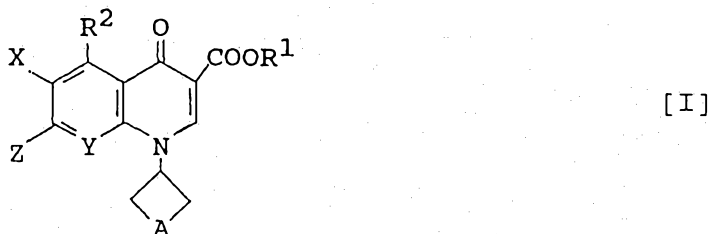


[Table 20]

Comp'd. No.	R ²	Z	Y	Appearance	Melting point (°C)	[Solvent] ¹ H-NMR	Reaction solvent
275	H	HN-	-N=	Colorless powder	≥270 Colored ≥300	[DMSO-d ₆]: 3.17(brs, 4H), 3.3-3.7(m, 2H), 4.02(brs, 4H), 4.1-4.35(m, 2H), 6.05-6.35(m, 1H), 8.14(d, J=12.7Hz, 1H), 8.86(s, 1H)	CHCl ₃
276	H	O-	-N=	Colorless powder	280-285	[DMSO-d ₆]: 3.3-3.6(m, 2H), 3.79(brs, 4H), 3.89(brs, 4H), 4.05-4.25(m, 2H), 6.1-6.25(m, 1H), 8.12(d, J=12.2Hz, 1H), 8.85(s, 1H)	CHCl ₃
277	H	S-	-N=	Pale yellow powder	274-283	[DMSO-d ₆]: 2.8(brs, 4H), 3.35-3.6(m, 2H), 4.02-4.35(m, 6H), 6.05-6.25(m, 1H), 8.11(d, J=13.67Hz, 1H), 8.84(s, 1H)	CHCl ₃
278	H	 (R) form	-N=	Pale yellow powder	≥260 Colored and decomposed	[DMSO-d ₆]: 1.8-2.05(m, 1H), 2.05-2.25(m, 1H), 3.4-4.1(m, 6H), 4.12-4.4(m, 2H), 6.0-6.2(m, 1H), 7.97(d, J=13Hz, 1H), 8.73(s, 1H)	CHCl ₃ + Et ₃ N
279	H	 (S) form	-N=	Pale yellow powder	≥260 Colored and decomposed	[DMSO-d ₆]: 1.8-2.0(m, 1H), 2.0-2.25(m, 1H), 3.4-4.1(m, 6H), 4.1-4.4(m, 2H), 6.0-6.25(m, 1H), 7.95(d, J=12Hz, 1H), 8.73(s, 1H)	CHCl ₃ + Et ₃ N
280	H	 Trans(-) form	-N=	Pale yellow powder	≥270 Colored ≥300	[DMSO-d ₆]: 1.05(d, J=7.3Hz, 3H), 2.2-2.45(m, 1H), 3.7-4.05(m, 3H), 4.1-4.25(m, 2H), 6.0-6.35(m, 1H), 7.99(d, J=13.2Hz, 1H), 8.76(s, 1H)	CHCl ₃ + Et ₃ N
281	H	HN-	-N=	Colorless solid	260-270	[DMSO-d ₆]: 1.24(d, 3H), 2.95-3.6(m, 7H), 4.15-4.35(m, 2H), 4.45-4.7(m, 2H), 6.1-6.25(m, 1H), 8.15(d, J=13.7Hz, 1H), 8.87(s, 1H)	CHCl ₃ + Et ₃ N

~~CLAIMS~~ The claims defining the invention are as follows:

- 1 1. A quinolone derivative represented by the follow-
2 ing formula [I] or a salt thereof:



4 wherein R¹ means a hydrogen atom or a carboxyl-protecting
5 group; R² denotes a hydrogen or halogen atom or a hydroxyl,
6 lower alkoxy, amino, aralkylamino, or mono- or di-(lower
7 alkyl)amino group; A represents an oxygen or sulfur atom or
8 N-R³ in which R³ is a hydrogen atom or an amino-protecting
9 group; X is a hydrogen or halogen atom; Y means a nitrogen
10 atom or C-R⁴ in which R⁴ is a hydrogen or halogen atom or a
11 lower alkyl or lower alkoxy group; and Z denotes a halogen
12 atom or a substituted or unsubstituted heterocyclic group
13 having at least one nitrogen atom as a hetero atom.

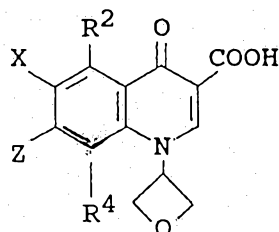
1 2. A compound as defined in claim 1 wherein A is an
2 oxygen atom.

1 3. A compound as defined in claim 2 wherein Y is the
2 formula: C-R⁴ in which R⁴ is a hydrogen or halogen atom.

1 4. A compound as defined in claim 3 wherein R¹ is a
2 hydrogen atom, X is a halogen atom and R² is a hydrogen atom
3 or amino group.

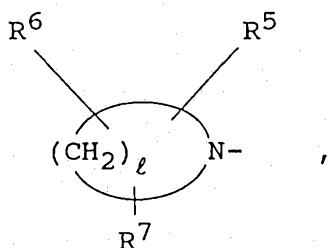


5. A quinolone derivative represented by the following formula or a salt thereof:



wherein R² denotes a hydrogen or an amino group, X is a halogen atom, R⁴ is a hydrogen or halogen atom and Z is a substituted or unsubstituted saturated 4-6 membered heterocyclic group having at least one nitrogen atom as a hetero atom.

6. A compound as defined in claim 5 wherein Z is a group of the formula:



wherein R⁵, R⁶ and R⁷ may be the same or different and individually denote a hydrogen or halogen atom or a hydroxyl, amino, lower alkyl, substituted or unsubstituted mono- or di-(lower alkyl)amino, cyclo(lower alkyl)amino, ~~lower~~ ^{amino-lower} alkyl, substituted or unsubstituted mono- or di-(lower alkyl)amino-lower alkyl, cyclo(lower alkyl)amino-lower alkyl, substituted or unsubstituted alkoxyl, substituted or

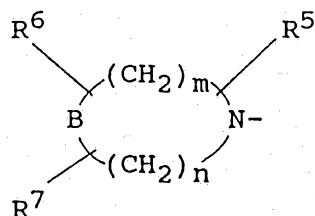


11 unsubstituted acyloxy, lower alkylthio, substituted or un-
 12 substituted aryl, cyano-lower alkyl, substituted or un-
 13 substituted acylamino, substituted or unsubstituted alkoxy-
 14 carbonyl, substituted or unsubstituted aminocyclo-lower
 15 alkyl, substituted or unsubstituted acylamino-lower alkyl,
 16 substituted or unsubstituted alkoxy-carbonylamino-lower
 17 alkyl, hydroxy-lower alkyl, substituted or unsubstituted
 18 alkoxy-lower alkyl, lower alkenyl, cyano, mercapto, or lower
 19 alkylimido-ylamino group, and ℓ is 3, 4 or 5.

1 7. A compound as defined in claim 6 wherein Z is pyr-
 2 rolidine which is substituted with one or two substituents
 3 independently selected from the group consisting of halogen
 4 atoms and nitro, hydroxyl, amino and lower alkyl groups.

1 8. The compound as defined in claim 7 which is 5-
 2 amino-7-(3-amino-4-methylpyrrolidin-1-yl)-6,8-difluoro-1-
 3 (oxetan-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, *or a salt thereof*

1 9. A compound as defined in claim 5 wherein Z is a
 2 group of the formula:



4 wherein B means an oxygen atom, a sulfur atom, $-\text{NR}^{10}-$ or

5 $\begin{array}{c} \text{O} \quad \text{R}^{10} \\ \parallel \quad | \\ -\text{C}-\text{N}- \end{array}$
 6 in which R^{10} is a hydrogen atom, substituted or



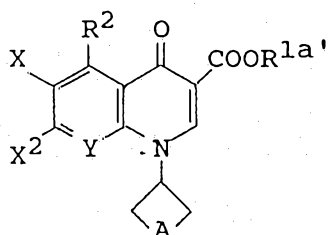
7 unsubstituted^{lower} alkyl group, substituted or unsubstituted
 8 cyclo-lower alkyl group, substituted or unsubstituted
 9 aralkyl group, substituted or unsubstituted aryl group, or
 10 substituted or unsubstituted^{lower} alkenyl group, R⁵, R⁶ and R⁷
 11 may be the same or different and individually denote a
 12 hydrogen or halogen atom or a hydroxyl, amino, lower alkyl,
 13 substituted or unsubstituted mono- or di-(lower alkyl)amino,
 14 cyclo(lower alkyl)amino, ^{amino-lower}~~lower~~ alkyl, substituted or un-
 15 substituted mono- or di-(lower alkyl)amino-lower alkyl,
 16 cyclo(lower alkyl)amino-lower alkyl, substituted or un-
 17 substituted alkoxy, substituted or unsubstituted acyloxy,
 18 lower alkylthio, substituted or unsubstituted aryl, cyano-
 19 lower alkyl, substituted or unsubstituted acylamino, sub-
 20 stituted or unsubstituted alkoxycarbonyl, substituted or un-
 21 substituted aminocyclo-lower alkyl, substituted or un-
 22 substituted acylamino-lower alkyl, substituted or un-
 23 substituted alkoxycarbonylamino-lower alkyl, hydroxy-lower
 24 alkyl, substituted or unsubstituted alkoxy-lower alkyl,
 25 lower alkenyl, cyano, mercapto, or lower alkylimidoylamino
 26 group, m is 1 or 2, and ^{n is 1 or 2.}~~t is 3, 4 or 5.~~

1 10. A compound as defined in claim 9 wherein Z is
 2 piperazine which may be substituted with one or two sub-
 3 stituents independently selected from the group consisting
 4 of halogen atoms and nitro, hydroxyl, amino and lower alkyl
 5 groups.

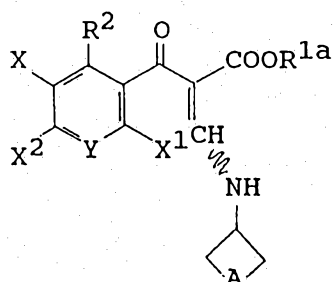


1 11. The compound as defined in claim 10 which is 5-
2 amino-6,8-difluoro-7-(4-methylpiperazin-1-yl)-1-(oxetan-3-
3 yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, *or a salt thereof.*

1 12. A process for the preparation of a quinolone
2 derivative represented by the following formula or a salt
3 thereof:

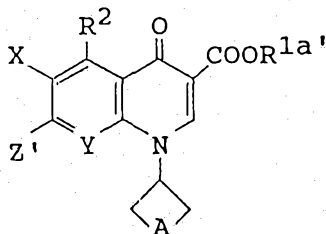


5 wherein R^{1a'} means a hydrogen atom or a lower alkyl group;
6 R² denotes a hydrogen or halogen atom or a hydroxyl, lower
7 alkoxyl, amino, aralkylamino, or mono- or di-(lower alkyl)-
8 amino group; A represents an oxygen or sulfur atom or N-R³
9 in which R³ is a hydrogen atom or an amino-protecting group;
10 X is a hydrogen or halogen atom; X² means a halogen atom;
11 and Y means a nitrogen atom or C-R⁴ in which R⁴ is a
12 hydrogen or halogen atom or a lower alkyl or lower alkoxyl
13 group, which comprises cyclizing a compound represented by
14 the following formula:



16 wherein R^{1a} means a lower alkyl group; X^1 denotes a halogen
 17 atom; and R^2 , A, X, X^2 and Y have the same meanings as
 18 defined above; and optionally removing the ester residual
 19 group and/or amino-protecting group; and when the salt is
 20 desired, converting the thus-cyclized product into the salt
 21 by a method known *per se* in the art.

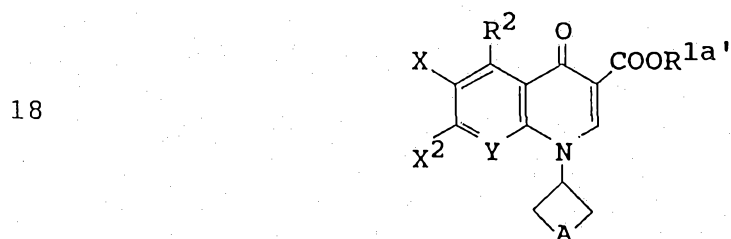
1 13. A process for the preparation of a quinolone
 2 derivative represented by the following formula or a salt
 thereof:



4 wherein $R^{1a'}$ means a hydrogen atom or a lower alkyl group;
 5 R^2 denotes a hydrogen or halogen atom or a hydroxyl, lower
 6 alkoxy, amino, aralkylamino, or mono- or di-(lower alkyl)-
 7 amino group; A represents an oxygen or sulfur atom or $N-R^3$
 8 in which R^3 is a hydrogen atom or an amino-protecting group;
 9 X is a hydrogen or halogen atom; Y means a nitrogen atom or
 10 $C-R^4$ in which R^4 is a hydrogen or halogen atom or a lower
 11 alkyl or lower alkoxy group; and Z' is a substituted or un-
 12 substituted heterocyclic group having at least one nitrogen
 13 atom as a hetero atom, which comprises reacting a compound
 14 represented by the following formula:

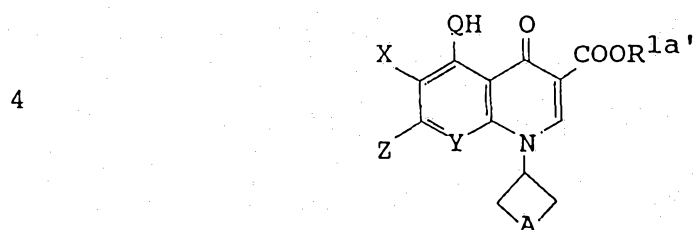


16 wherein Z' has the same meaning as defined above, with a
17 compound represented by the following formula:



19 wherein X² denotes a halogen atom; and R¹ᵃ', R², A, X and Y
20 have the same meanings as defined above; and optionally
21 removing the ester residual group and/or amino-protecting
22 group; and when the salt is desired, converting the reaction
23 product into the salt by a method known *per se* in the art.

1 14. A process for the preparation of a quinolone
2 derivative represented by the following formula or a salt
3 thereof:

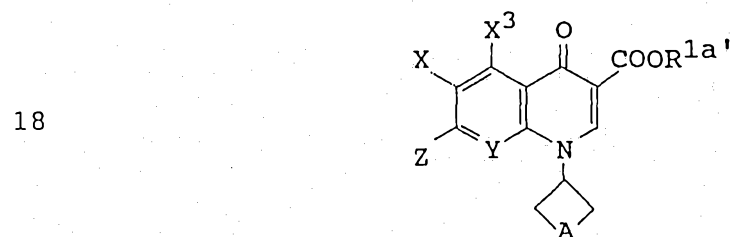


5 wherein R¹ᵃ' means a hydrogen atom or a lower alkyl group; A
6 represents an oxygen or sulfur atom or N-R³ in which R³ is a
7 hydrogen atom or an amino-protecting group; Q represents -O-
8 , -NH- or -NR¹⁶- in which R¹⁶ is a lower alkyl group; X is a
9 hydrogen or halogen atom; Y means a nitrogen atom or C-R⁴ in
10 which R⁴ is a hydrogen or halogen atom or a lower alkyl or

11 lower alkoxyl group; and Z is a halogen atom or a sub-
12 stituted or unsubstituted heterocyclic group having at least
13 one nitrogen atom as a hetero atom, which comprises reacting
14 a compound represented by the following formula:

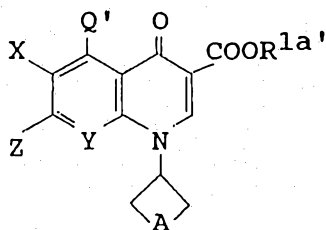


16 wherein Q has the same meaning as defined above, with a com-
17 pound represented by the following formula:



19 wherein X^3 denotes a halogen atom; and $R^{1a'}$, A, X, Y and Z
20 have the same meanings as defined above; removing the benzyl
21 group from the reaction product thus formed; and optionally
22 removing the ester residual group and/or amino-protecting
23 group; and when the salt is desired, converting the
24 resultant benzyl-free product into the salt by a method
25 known *per se* in the art.

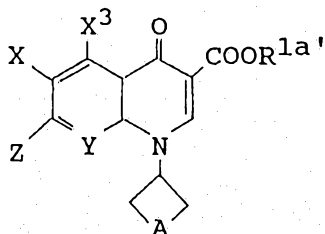
1 15. A process for the preparation of a quinolone
2 derivative represented by the following formula or a salt
3 thereof:



4
5 wherein $R^{1a'}$ means a hydrogen atom or a lower alkyl group; A
6 represents an oxygen or sulfur atom or $N-R^3$ in which R^3 is a
7 hydrogen atom or an amino-protecting group; Q' represents a
8 hydroxyl, lower alkoxyl, amino, aralkylamino, or mono- or
9 di-(lower alkyl)amino group; X is a hydrogen or halogen
10 atom; Y means a nitrogen atom or $C-R^4$ in which R^4 is a
11 hydrogen or halogen atom or a lower alkyl or lower alkoxyl
12 group; and Z is a halogen atom or a substituted or un-
13 substituted heterocyclic group having at least one nitrogen
14 atom as a hetero atom, which comprises reacting a compound
15 represented by the following formula:



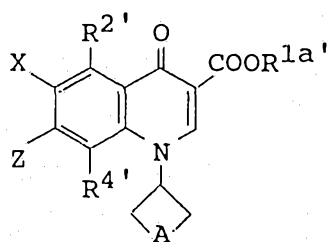
16
17 wherein Q' has the same meaning as defined above, with a
18 compound represented by the following formula:



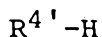
19
20 wherein X^3 denotes a halogen atom; and $R^{1a'}$, A, X, Y and Z
21 have the same meanings as defined above; and optionally

22 removing the ester residual group and/or amino-protecting
23 group; and when the salt is desired, converting the
24 resultant product into the salt by a method known *per se* in
25 the art.

1 16. A process for the preparation of a quinolone
2 derivative represented by the following formula or a salt
3 thereof:

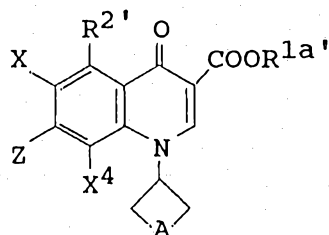


5 wherein R^{1a'} means a hydrogen atom or a lower alkyl group;
6 R^{2'} denotes a hydrogen atom or a hydroxyl, lower alkoxyl,
7 amino, aralkylamino, or mono- or di-(lower alkyl)amino
8 group; R^{4'} represents a lower alkoxyl group; A denotes an
9 oxygen or sulfur atom or N-R³ in which R³ is a hydrogen atom
10 or an amino-protecting group; X means a hydrogen or halogen
11 atom; and Z is a halogen atom or a substituted or un-
12 substituted heterocyclic group having at least one nitrogen
13 atom as a hetero atom, which comprises reacting a compound
14 represented by the following formula:



15
16 wherein R^{4'} has the same meaning as defined above, with a
17 compound represented by the following formula:

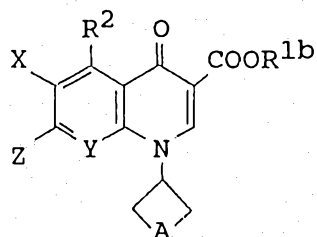
18



19 wherein X⁴ denotes a halogen atom; and R^{1a'}, R^{2'}, A, X and Z
 20 have the same meanings as defined above; and optionally
 21 removing the ester residual group and/or amino-protecting
 22 group; and when the salt is desired, converting the reaction
 23 product into the salt by a method known *per se* in the art.

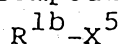
1 17. A process for the preparation of a quinolone
 2 derivative represented by the following formula or a salt
 3 thereof:

4

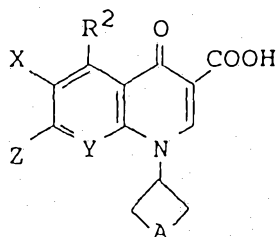


5 wherein R^{1b} means a carboxyl-protecting group; R² denotes a
 6 hydrogen or halogen atom or a hydroxyl, lower alkoxyl,
 7 amino, aralkylamino, or mono- or di-(lower alkyl)amino
 8 group; A represents an oxygen or sulfur atom or N-R³ in
 9 which R³ is a hydrogen atom or an amino-protecting group; X
 10 is a hydrogen or halogen atom; Y means a nitrogen atom or C-
 11 R⁴ in which R⁴ is a hydrogen or halogen atom or a lower
 12 alkyl or lower alkoxyl group; and Z is a halogen atom or a

substituted or unsubstituted heterocyclic group having at least one nitrogen atom as a hetero atom, which comprises reacting a compound represented by the following formula:



wherein X^5 means a halogen atom and R^{1b} has the same meaning as defined above, with a compound represented by the following formula:



wherein R^2 , A, X, Y and Z have the same meanings as defined above; and when the salt is desired, converting the reaction product into the salt by a method known per se in the art.

18. An antibacterial agent comprising as an active ingredient the quinolone derivative or the salt thereof according to claim 1 and a pharmaceutically acceptable carrier.

19. A method of inhibiting bacterial growth comprising administering to a patient in need an effective amount of an antibacterial agent according to claim 18.

20. A quinolone derivative according to claim 1 or 5 substantially as hereinbefore described with reference to any one of the examples.

21. A process according to any one of claims 12 to 17 substantially as hereinbefore described with reference to any one of the examples.

DATED: 2 March 1992

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