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Sawa

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(54) **METHOD FOR STABILIZING ARYL CARBOXYLIC ACID, STABILIZER THEREOF AND AQUEOUS SOLUTION CONTAINING STABILIZED ARYL CARBOXYLIC ACID**

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This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.** **514/291**; 514/230.5; 514/253.04; 514/253.08; 514/264; 514/300; 514/312; 514/352; 514/365; 514/420; 514/567; 514/226.2

(58) **Field of Search** 546/89, 311, 204, 546/500, 501; 544/38; 514/291, 226.2, 352, 365, 420, 567, 264, 300, 253.08, 312, 230.5, 253.04

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(57) **ABSTRACT**

A method for stabilizing an arylcarboxylic acid, which comprises adding a heterocyclic base to the arylcarboxylic acid or a pharmacologically acceptable salt thereof, a stabilizer thereof and an aqueous solution containing a stabilized arylcarboxylic acid. According to the stabilization method of the present invention, arylcarboxylic acid and pharmacologically acceptable salts thereof, particularly pranopfen, can be stabilized at every temperature range, particularly at lower temperatures, thereby making the production of an aqueous solution to be used as an eye drop, nasal drop, ear drop and the like possible.

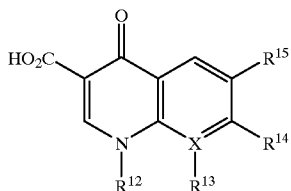
7 Claims, No Drawings

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wherein

X is as defined above; and

R^{12} , R^{13} , R^{14} and R^{15} may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

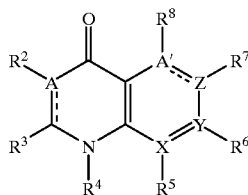
wherein R^{12} and R^{13} may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^{14} and R^{15} may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R^{13} is void, or a pharmacologically acceptable salt thereof.

(5) The method of (4) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosufloxacin.

(6) The method of (1) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, alclofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclazic acid.

(7) The method of (1) above, wherein the heterocyclic base is added in a proportion of 0.001–5 parts by weight per 100 parts by weight of the arylcarboxylic acid.

(8) A stabilizer of an arylcarboxylic acid or a pharmacologically acceptable salt thereof, which comprises, as an active ingredient, a heterocyclic base of the formula (II):



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group, wherein R^4 and R^5 may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X,

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(IV)

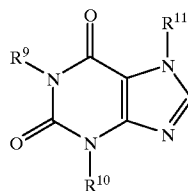
and R^6 and R^7 may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R^5 is void; and

5 --- is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH, and = is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and --- is a single bond.

(9) The stabilizer of (8) above, wherein the heterocyclic base is a purine base of the formula (III):

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(III)



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wherein

R^9 , R^{10} and R^{11} may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

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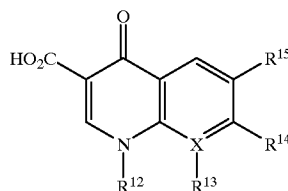
or a pharmacologically acceptable salt thereof.

(10) The stabilizer of (9) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.

(11) The stabilizer of (8) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (IV):

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(IV)



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wherein

X is as defined above; and

R^{12} , R^{13} , R^{14} and R^{15} may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

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wherein R^{12} and R^{13} may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^{14} and R^{15} may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R^{13} is void, or a pharmacologically acceptable salt thereof.

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(12) The stabilizer of (11) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosufloxacin.

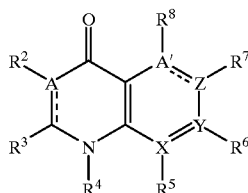
(13) The stabilizer of (8) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, aldlofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclazic acid.

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- (14) The stabilizer of (8) above, wherein the heterocyclic base is contained in a proportion of 0.001–5 parts by weight per 100 parts by weight of the arylcarboxylic acid.
- (15) An aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof stabilized by the method of (1) above and a heterocyclic base of the formula (II):



wherein

A and A' are each a carbon atom or a nitrogen atom;

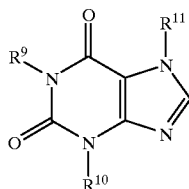
X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group, wherein R⁴ and R⁵ may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R⁶ and R⁷ may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R⁵ is void; and

— is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH and = is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and — is a single bond.

- (16) The aqueous solution of (15) above, wherein the heterocyclic base is a purine base of the formula (III):



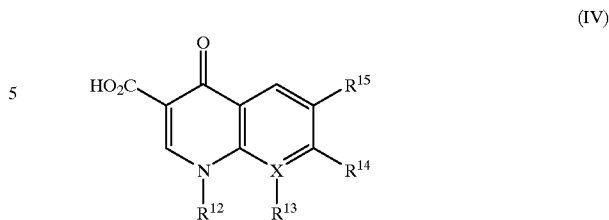
wherein

R⁹, R¹⁰ and R¹¹ may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

or a pharmacologically acceptable salt thereof.

- (17) The aqueous solution of (16) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.
- (18) The aqueous solution of (15) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (IV):

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(II) 10

wherein

X is as defined above; and

R¹², R¹³, R¹⁴ and R¹⁵ may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

wherein R¹² and R¹³ may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R¹⁴ and R¹⁵ may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R¹³ is void, or a pharmacologically acceptable salt thereof.

- (19) The aqueous solution of (18) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosulofloxacin.

- (20) The aqueous solution of (15) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, alclofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclazic acid.

- (21) The aqueous solution of any one of the above (15) to (20), which is an eye drop.

- (22) The aqueous solution of any one of the above (15) to (20), which is a nasal drop.

- (23) The aqueous solution of any one of the above (15) to (20), which is an ear drop.

(III) 45

DETAILED DESCRIPTION OF THE INVENTION

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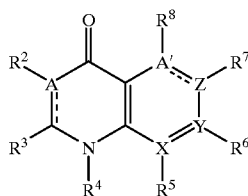
The stabilizing method of the present invention comprises the addition of a stabilizer containing a heterocyclic base as an active ingredient to an arylcarboxylic acid, which is an acidic compound and which has an antiinflammatory activity, or a pharmacologically acceptable salt thereof. For example, a heterocyclic base is added to an arylcarboxylic acid or a pharmacologically acceptable salt thereof.

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To be specific, an arylcarboxylic acid and a heterocyclic base are dissolved in water and the pH thereof is adjusted with boric acid, acetic acid, phosphoric acid and the like, which is followed by lyophilization where necessary.

While the pH varies depending on the kind of arylcarboxylic acid, it is generally 5–9, preferably about 6–8.

Said heterocyclic base may be any as long as it has the following formula (II):



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may
combinedly form CH;

R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ may be the same or different
and each is a hydrogen atom, a halogen, a carboxyl
group, an optionally substituted lower alkyl group, an
optionally substituted cycloalkyl group, an optionally
substituted aryl group or an optionally substituted heterocyclic group,
wherein R⁴ and R⁵ may form a 4- to 6-membered hetero-
cyclic group with the adjacent nitrogen atom and X,
and R⁶ and R⁷ may form a 4- to 6-membered hetero-
cyclic group with the adjacent Y and Z, provided that
when X is a nitrogen atom, R⁵ is void; and

— is a single bond or a double bond, provided that
when A is a carbon atom, Y and Z are each CH and
= is a double bond, and when A is a nitrogen atom,
Y and Z combinedly form CH and — is a single
bond.

The alkyl of the “optionally substituted lower alkyl
group” has 1 to 6 carbon atoms, and may be a linear or
branched one, such as methyl, ethyl, propyl, isopropyl,
butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-
pentyl, hexyl, isohexyl, neohexyl and the like.

The cycloalkyl of the “optionally substituted cycloalkyl
group” has 3 to 9 carbon atoms, and is exemplified by
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohep-
tyl and the like.

The substituents of the above-mentioned lower alkyl
group and cycloalkyl group include lower alkyl group,
halogen and the like.

The lower acyl of the “optionally substituted lower acyl
group” may be, for example, formyl group, acetyl group,
propionyl group, butyryl group, isobutyryl group, valeryl
group, benzoyl group, naphthoyl group, toluoyl group, sali-
cyloyl group and the like.

The above-mentioned acyl may be substituted by suitable
substituents which may be the same or different, such as
lower alkyl (e.g., methyl, ethyl, propyl, etc.);
lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g., methylthio, ethylthio, etc.);
lower alkylamino (e.g., methylamino, ethylamino, propyl-
amino and the like);
cyclo(lower)alkyl such as cyclo(C₃–C₆)alkyl (e.g.,
cyclopentyl, cyclohexyl and the like);
cyclo(lower)alkenyl such as cyclo(C₃–C₆)alkenyl (e.g.,
cyclohexenyl, cyclohexadienyl and the like);
halogen (e.g., fluorine, chlorine, bromine and iodine);
amino; amino protecting group; hydroxy; protected
hydroxy; cyano; nitro; carboxy; protected carboxy;
sulfo; sulfamoyl; imino; oxo;
amino(lower)alkyl (e.g., aminomethyl, aminoethyl and
the like), carbamoyloxy, hydroxy(lower)alkyl (e.g.,

(ii) hydroxymethyl, 1- or 2-hydroxyethyl, 1- or 2- or
3-hydroxypropyl and the like); and the like.

The aryl of the “optionally substituted aryl group” is
exemplified by phenyl, naphthyl and the like, with prefer-
ence given to naphthyl.

The heterocyclic group of the optionally substituted hetero-
cyclic group may contain, besides the carbon atom, at
least one hetero atom selected from the group consisting of
a nitrogen atom, sulfur atom and oxygen atom, as the atom
constituting the ring, and may be a saturated or unsaturated,
heteromonocyclic or heteropolycyclic group.

The preferable heterocyclic groups are the following:

3- to 6-membered unsaturated heteromonocyclic group
having 1 to 4 nitrogen atoms, such as pyrrolyl,
pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl,
pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-
triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl and the
like), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl and
the like), triazinyl (e.g., 1,2,4-triazinyl and the like),
and the like;

3- to 7-membered saturated heteromonocyclic group hav-
ing 1 to 4 nitrogen atoms, such as pyrrolidinyl,
imidazolidinyl, piperidinyl, piperazinyl,
homopiperazinyl, and the like;

saturated heteropolycyclic group having 1 to 4 nitrogen
atoms, such as quinuclidinyl and the like;

unsaturated heteropolycyclic group having 1 to 5 nitrogen
atoms, such as indolyl, isoindolyl, 3H-indolyl,
indoliziny, benzoimidazolyl, quinolyl, isoquinolyl,
indazolyl, phthalazinyl, naphthyridinyl, quinoxalinyl,
quinazolinyl, cinnolyl, benzotriazolyl, tetrazolo-
pyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl and the
like), pteridinyl, carbazolyl, phenanthridinyl, acridinyl,
perimidyl, and the like;

3- to 6-membered unsaturated heteromonocyclic group
having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms,
such as oxazolyl, isooxazolyl, oxadiazolyl (e.g., 1,2,4-
oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl and
the like), and the like;

3- to 6-membered saturated heteromonocyclic group hav-
ing 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such
as morpholinyl, sydnolyl, and the like;

unsaturated condensed heterocyclic group having 1 to 3
nitrogen atoms and 1 or 2 oxygen atoms, such as
benzofurazanyl, benzoxazolyl, benzoxazinyl,
benzoxadiazolyl, and the like;

3- to 6-membered unsaturated condensed heterocyclic
group having 1 to 3 nitrogen atoms and 1 or 2 sulfur
atoms, such as thiazolyl, isothiazolyl, thiadiazolyl (e.g.,
1,,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-
thiadiazolyl and the like), and the like;

3- to 6-membered saturated heteromonocyclic group hav-
ing 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such
as thiazolidinyl and the like;

unsaturated condensed heterocyclic group having 1 to 3
nitrogen atoms and 1 or 2 sulfur atoms, such as
benzothiazolyl, benzothiadiazolyl, and the like;

3- to 6-membered unsaturated heteromonocyclic group
having 1 oxygen atom, such as furyl, pyranyl and the
like;

3- to 6-membered unsaturated heteromonocyclic group
having 1 or 2 sulfur atoms, such as thienyl,
dihydrothienyl, and the like;

unsaturated condensed heterocyclic group having 1 or 2
sulfur atoms, such as benzothienyl and the like; and the
like.

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