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**Sawa**

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

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This patent is subject to a terminal disclaimer.

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**A61K 31/52; A61K 47/22**

(52) **U.S. Cl.** ..... **514/291; 514/230.5; 514/253.04;**  
**514/253.08; 514/264; 514/300; 514/312;**  
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**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**

Petitioner InnoPharma EX 1087  
IPR2015-00902  
IPR2015-00903

**METHOD FOR STABILIZING  
ARYLCARBOXYLIC ACID, STABILIZER  
THEREOF AND AQUEOUS SOLUTION  
CONTAINING STABILIZED  
ARYLCARBOXYLIC ACID**

**TECHNICAL FIELD OF THE INVENTION**

The present invention relates to a method for stabilizing arylcarboxylic acid, which is an acidic compound and which has an antiinflammatory activity, or a pharmacologically acceptable salt thereof, a stabilizer thereof and an aqueous solution containing a stabilized arylcarboxylic acid.

**BACKGROUND OF THE INVENTION**

Arylcarboxylic acid and pharmacologically acceptable salts thereof have been known to be extremely superior antiinflammatory agents. However, said arylcarboxylic acids, particularly pranoprofen, diclofenac and bromfenac, are associated with a problem that they become unstable in an aqueous solution.

Arylcarboxylic acid and pharmacologically acceptable salts thereof have been also known to be stabilized by adding an antioxidant, by adjusting the pH, concentration and ionic strength thereof, by shutting out the light, and the like. These methods, nevertheless, cannot provide sufficient stability at lower temperatures.

Thus, an aqueous solution has not been provided which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, diclofenac or bromfenac, and which has sufficient stability at lower temperatures.

While WO9632941 A1 discloses pranoprofen combined with an organic amine, it does not disclose the heterocyclic base to be used in the present invention.

**SUMMARY OF THE INVENTION**

It is therefore an object of the present invention to provide a method for stabilizing an arylcarboxylic acid and a pharmacologically acceptable salt thereof.

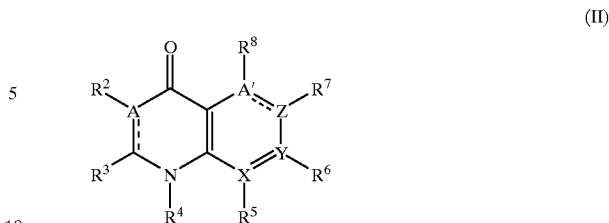
Another object of the present invention is to provide a stabilizer of an arylcarboxylic acid and a pharmacologically acceptable salt thereof, which contains a heterocyclic base.

Yet another object of the present invention is to provide an aqueous solution containing a solubilized arylcarboxylic acid and a heterocyclic base.

According to the present invention, it has now been found that the addition of a heterocyclic base to an arylcarboxylic acid or a pharmacologically acceptable salt thereof leads to successful stabilization thereof, particularly pranoprofen, at every temperature range, particularly at low temperatures.

Thus, the present invention provides the following.

(1) A method for stabilizing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, which comprises adding 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<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> 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<sup>4</sup> and R<sup>5</sup> may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R<sup>6</sup> and R<sup>7</sup> may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R<sup>5</sup> 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,

to an arylcarboxylic acid of the formula (I):



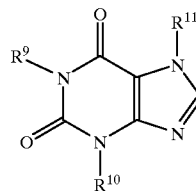
wherein

L<sup>1</sup> is an optionally substituted heterocyclic group or aryl group having not more than 14 carbon atoms; and

R<sup>1</sup> is an optionally substituted alkyl group having not more than 4 carbon atoms or a single bond, or a pharmacologically acceptable salt thereof.

(2) The method of (1) above, wherein the heterocyclic base is a purine base of the formula (III):

(III)



wherein

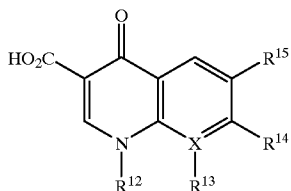
R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

or a pharmacologically acceptable salt thereof.

(3) The method of (2) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.

(4) The method of (1) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (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;

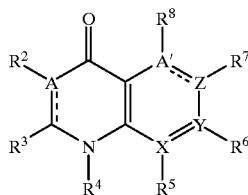
wherein  $R^{12}$  and  $R^{13}$  may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and  $R^{14}$  and  $R^{15}$  may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom,  $R^{13}$  is void, or a pharmacologically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

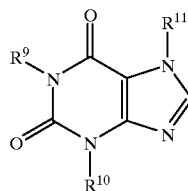
and  $R^6$  and  $R^7$  may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom,  $R^5$  is void; and

5  $\equiv$  is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH, and  $\equiv$  is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and  $\equiv$  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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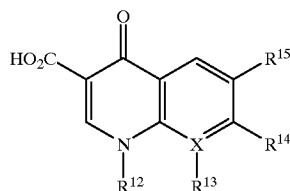
or a pharmacologically acceptable salt thereof.

(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.

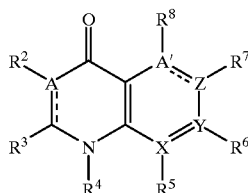
(13) The stabilizer of (8) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, aldlofenac, flurbiprofen, 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;

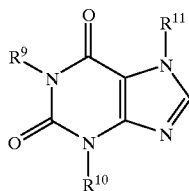
Y and Z are each a carbon atom or Y and Z may combinedly form CH;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> 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<sup>4</sup> and R<sup>5</sup> may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R<sup>6</sup> and R<sup>7</sup> may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R<sup>5</sup> 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):



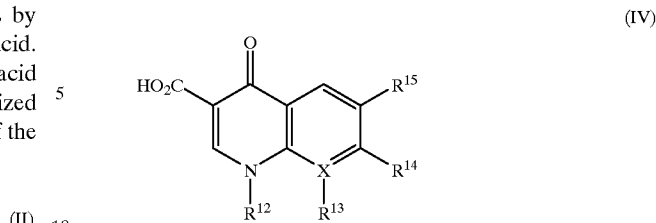
wherein

R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> 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)

wherein

X is as defined above; and

R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> 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<sup>12</sup> and R<sup>13</sup> may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R<sup>14</sup> and R<sup>15</sup> may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R<sup>13</sup> 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 tosulfoxacin.
- (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.

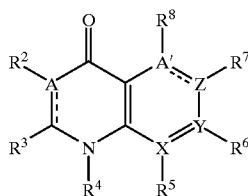
#### DETAILED DESCRIPTION OF THE INVENTION

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.

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;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> 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, an optionally substituted aryl  
group or an optionally substituted heterocyclic group,  
wherein R<sup>4</sup> and R<sup>5</sup> may form a 4- to 6-membered hetero-  
cyclic group with the adjacent nitrogen atom and X,  
and R<sup>6</sup> and R<sup>7</sup> may form a 4- to 6-membered hetero-  
cyclic group with the adjacent Y and Z, provided that  
when X is a nitrogen atom, R<sup>5</sup> 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(C<sub>3</sub>–C<sub>6</sub>)alkyl (e.g.,  
cyclopentyl, cyclohexyl and the like);  
cyclo(lower)alkenyl such as cyclo(C<sub>3</sub>–C<sub>6</sub>)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, quinoxaliny,  
quinazolinyl, cinnoliny, 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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Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

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

## API

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

## LAW FIRMS

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

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

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.