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(2-IMIDAZOLIN-2-YLAMINO) QUINOXALINE DERIVATIVES AND METHODS FOR USING SAME.

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Description

Related Application

This application is a continuation-in-part of co-pending patent application Serial No. 420,817, filed October 12, 1989.

Background of the Invention

The present invention relates to novel substituted derivatives of quinoxaline. More particularly, the invention relates to such derivatives which are useful as therapeutic agents, for example, to effect reduction in intraocular pressure, to increase renal fluid flow and to effect an alteration in the rate of fluid transport in the gastrointestinal tract.

Various quinoxaline derivatives have been suggested as therapeutic agents. For example, Danielewicz, et al U.S. Patent 3,880,319 discloses compounds as regulators of the cardiovascular system which have the following formula:

where the 2-imidazolin-2-yamino group may be in any of the 5-, 6-, 7- or 8- position of the quinoxaline nucleus; X, Y and Z may be in any of the remaining 5-6-, 7- or 8- positions and may be selected from hydrogen, halogen, lower alkyl, lower alkoxy or trifluoromethyl; and R is an optional substituent in either the 2- or 3- position of the quinoxaline nucleus and may be hydrogen, lower alkyl or lower alkoxy.

European patent publication no. 0 422 878 discloses certain 2-imidazolin-2-yamino tetrahydroquinoxalines as useful for reducing intraocular pressure, increasing renal fluid flow and affecting fluid transport in the gastrointestinal tract, which compounds have the following formula:

where \( R_1 \) and \( R_4 \) are H or \( C_1-C_4 \) alkyl, \( R_2 \) and \( R_3 \) are H, oxo or \( C_1-C_4 \) alkyl, the 2-imidazolin-2-yamino group being in the 5-, 6-, 7- or 8- position of the quinoxaline nucleus, and \( R_5, R_6 \) and \( R_7 \) each is located in one of the remaining 5-, 6-, 7- or 8- positions of the quinoxaline nucleus and is Cl, Br, H or \( C_1-C_3 \) alkyl.
Summary of the Invention

The novel compounds of the present invention are those having the formula:

\[
\begin{align*}
&N = N \\
&\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{R}_5 \quad \text{R}_6 \quad \text{R}_7
\end{align*}
\]

and pharmaceutically acceptable acid addition salts thereof, wherein \(\text{R}_1\) and \(\text{R}_4\) are independently selected from the group consisting of \(H\) and alkyl radicals having 1 to 4 carbon atoms; the \(\text{R}_2\) and \(\text{R}_3\) are each \(H\) or alkyl radicals having 1 to 4 carbon atoms or are, together, \(\text{o xo}\); the \(\text{R}_5\) are each \(H\) or alkyl radicals having 1 to 4 carbon atoms or are, together, \(\text{o xo}\), provided that the \(\text{R}_2\) or the \(\text{R}_3\) are alkyl radicals; the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- positions of the quinoxaline nucleus; and \(\text{R}_1\), \(\text{R}_6\) and \(\text{R}_7\) each is located in one of the remaining 5-, 6-, 70 or 8- positions of the quinoxaline nucleus and is independently selected from the group consisting of \(\text{Cl}, \text{Br}, \text{H}\) and alkyl radicals having 1 to 3 carbon atoms.

Particularly useful compounds are those in which \(\text{R}_1\) and \(\text{R}_4\) are \(H\), the 2-imidazolin-2-ylamino group is in the 6- position of the quinoxaline nucleus, \(\text{R}_6\) is selected from the group consisting of \(\text{Cl}, \text{Br}\) and alkyl radicals containing 1 to 3 carbon atoms, more preferably \(\text{Br}\), and is in the 5- position of the quinoxaline nucleus, and \(\text{R}_1\) and \(\text{R}_7\) are \(H\).

In one embodiment, the \(\text{R}_2\) or \(\text{R}_3\) are methyl radicals. The other of the \(\text{R}_2\) or \(\text{R}_3\), i.e., those that are not alkyl, e.g., methyl, radicals, are \(H\), or together is \(\text{o xo}\).

Pharmaceutically acceptable acid addition salts of the compounds of the invention are those formed from acids which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate and p-toluene sulphonate salts.

The present compounds provide one or more therapeutic effects, e.g., in mammals. Thus, these compounds are useful in a method for treating a mammal in which one or more of these compounds are administered to a mammal in an amount sufficient to provide the desired therapeutic effect in the mammal. Among the desired therapeutic effects provided by the present compounds include altering the rate of fluid transport in the gastrointestinal tract of a mammal; reducing or maintaining the intraocular pressure in at least one eye of a mammal; and increasing the renal fluid flow in at least one kidney of a mammal.

Detailed Description of the Invention

The compounds of the present invention, are as described above. All stereoisomers, tautomers and mixtures thereof which comply with the constraints of one or more formulae of the present compounds are included within the scope of the present invention. For example, both tautomers

\[
\text{and R}_{1} \quad \text{R}_{2} \quad \text{R}_{3} \quad \text{R}_{4} \quad \text{R}_{5} \quad \text{R}_{6} \quad \text{R}_{7}
\]

are within the scope of the present invention.

The present compounds may be prepared from available starting materials. For example, 4-nitro-1,2-phenylenediamine may be reacted with an appropriate halide substituted carbonyl halide, in particular, a bromide substituted carbonyl bromide. This reaction, which provides for substitution of one of the amine groups on the phenylene ring by the carbonyl halide, is preferably conducted in a solvent and preferably at a temperature in the range of about 10°C to about 50°C in particular about room temperature. Reaction
pressure is preferably such that the solvent is maintained substantially in the liquid phase. The reaction preferably occurs over a period of time in the range of about 2 hours to about 24 hours. Examples of useful solvents include methylene chloride (CH₂Cl₂), chloroform (CHCl₃), tetrahydrofuran and the like. A trialkyl amine, e.g., triethylamine, may be used as part of the solvent and/or to promote or facilitate the substitution reaction.

The resulting mixture of halo amide isomers are recovered preferably by conventional techniques, e.g., extraction, washing, drying, concentration, chromatography and the like, from the substitution reaction mixture. The isomers are then cyclized. This cyclization is preferably effected at a temperature in the range of about 10°C to about 50°C, in particular at room temperature, by contacting the isomers, preferably dissolved in a solvent such as methylene chloride, with a cyclizing agent, such as AgBF₄, AgNO₃ and the like. Reaction pressure is preferably such that the solvent is maintained substantially in the liquid phase. The reaction preferably occurs over a period of time in the range of about 1 hour to about 24 hours. Conventional techniques, e.g., such as noted above, can be used to recover the cyclized isomers. Chromatography can be used to separate the isomers and provide them in substantially pure form.

The cyclized compound produced as described above, identified as a nitro-substituted quinoxalinone, is hydrogenated to convert the nitro group to an amino group. This hydrogenation preferably occurs with the nitro-substituted quinoxalinone dissolved in a liquid, e.g., a lower alcohol such as methanol, ethanol or the like. A catalyst effective to promote the hydrogenation is preferably present. Examples of such catalysts include the platinum group metals, in particular palladium, platinum group metal compounds, such as platinum oxide, and mixtures thereof. Hydrogen, e.g., free molecular hydrogen, is present in an amount at least sufficient to provide the desired hydrogenation, preferably in an amount in excess of that required to provide the desired hydrogenation. The temperature and pressure at which the hydrogenation occurs are preferably selected to maintain the nitro-substituted quinoxalinone and hydrogenated product substantially in the liquid phase. Temperatures in the range of about 10°C to about 100°C and pressures in the range of about 0.5 atmospheres to about 5 atmospheres often provide acceptable results. These conditions are maintained for a time sufficient to provide the desired hydrogenation reaction. This period of time is often in the range of about 1 hour to about 16 hours. The hydrogenated product is separated from the hydrogenation reaction mixture and recovered, e.g., using conventional techniques.

At this point, the hydrogenated product may be subjected to one or more reactions to include one or more groups in the compound, as desired. For example, in one embodiment, it is preferred that the final quinoxaline derivative of the present invention includes at least one halide group, in particular a bromo group, on the aromatic ring structure. In order to provide such a bromo group, the above-noted hydrogenated product is brominated. Such bromination can occur by dissolving the hydrogenated product in a suitable solvent, e.g., glacial acetic acid, trifluoroacetic acid and the like, and contacting this solution with bromine. The mixture is preferably maintained at a suitably low temperature, e.g., in the range of about 10°C to about 50°C, so that the degree of bromination can be controlled. Cooling or removing heat from the reaction mixture may be desirable. Room temperature bromination provides satisfactory results. Reaction pressure is preferably such that the solvent is maintained substantially in the liquid phase. The reaction preferably occurs over a period of time in the range of about 0.25 hours to about 6 hours. Conventional techniques, e.g., vacuum filtration, can be used to recover the brominated product, which may be a hydrobromide salt.

The above-noted hydrogenated product or substituted hydrogenated product is reacted with 2-imidazoline-2-sulfonic acid to produce a 2-imidazolin-2-ylamino quinoxaline derivative of the present invention. Such derivatives include an oxo group. This reaction can occur by dissolving the reactants in an appropriate solvent, e.g., an alcohol such as isobutanol, and heating this solution to reflux at atmospheric pressure. Preferred reaction temperatures are in the range of about 70°C to about 150°C. Reaction pressure is preferably such that the solvent is refluxed or maintained substantially in the liquid phase. The reaction preferably occurs over a period of time in the range of about 1 hour to about 24 hours. Conventional techniques, e.g., concentration and chromatography, can be used to recover the desired quinoxaline derivative.

The present quinoxaline derivatives which do not include an oxo group can be obtained by reacting the above-described oxo-containing quinoxaline derivatives to remove the oxo group. This can be accomplished by dissolving the oxo-containing material in an appropriate solvent, e.g., tetrahydrofuran, acetic acid, trifluoroacetic acid, diethyl ether and the like, and subjecting this solution to a hydride reducing agent, such as LiAlH₄, NaBH₄, NaCNBH₃ and the like. Reaction temperatures in the range of about 20°C to about 100°C can be used. Conventional techniques, e.g., cooling, concentration and chromatography, can be employed to provide the present quinoxaline derivative which do not include an oxo group.
For compounds in which R₁ and/or R₂ are to be alkyl, the quinoxaline derivative (having no substituents corresponding to R₁ and R₂) may be reacted with a suitable hydride reducing agent in the presence of a selected aldehyde or aldehydes. The aldehyde or aldehydes used are selected based on the specific R₁ and/or R₂ alkyl group or groups desired. For example, if R₁ and/or R₂ is to be methyl, formaldehyde is used, if R₁ and/or R₂ is to be ethyl, acetaldehyde is used, etc. The temperature and pressures at which the reaction occurs are preferably selected to maintain the quinoxaline derivative and product in the liquid phase. Temperatures in the range of about 0°C to about 50°C and pressure in the range of about 0.5 atmospheres to about 2 atmospheres often provide acceptable results. The reaction time is often in the range of about 1 hour to about 24 hours. The amount of aldehyde used may vary depending on the final compound desired. A mixture of final compounds, i.e., a compound in which both R₁ and R₂ are alkyl mixed with compounds in which only one of R₁ or R₂ is alkyl, may be produced by the reaction. One or more individual quinoxaline derivatives of the present invention can be separated and recovered from this mixture, e.g., using conventional techniques.

The present compounds are useful to provide one or more desired therapeutic effects in a mammal. Among the desired therapeutic effects are an alteration, preferably a decrease, in the rate of fluid transport in the gastrointestinal tract of a mammal, a reduction in or maintenance of the intracocular pressure in at least one eye of a mammal; and an increase in the renal fluid flow in at least one kidney of a mammal. Thus, for example, the present compounds may be effective as an anti-diarrheal agent, a medication for use in the treatment or management of glaucoma, and/or a medication for use in the treatment or management of kidney disease. One important feature of many of the present compounds is that the desired therapeutic effect is achieved with reduced side effects, in particular with reduced effects on the blood pressure of the mammal to which the present compound is administered.

Any suitable method of administering the present compound or compounds to the mammal to be treated may be used. The particular method of administration chosen is preferably one which allows the present compound or compounds to have the desired therapeutic effect in an effective manner, e.g., low medication concentration and low incidence of side effects. In many applications, the present compound or compounds are administrated to a mammal in a manner substantially similar to that used to administer alpha agonists, in particular alpha 2 agonists, to obtain the same or a similar therapeutic effect. The present compound or compounds may be included in a medication composition together with one or more other components to provide a medication composition which can be effectively administered. Such other components, e.g., carriers, anti-oxidants, bulking agents and the like, may be chosen from those materials which are conventional and well known in the art, e.g., as being included in medication compositions with alpha 2 agonists.

The present compounds are often administered to the eye of a mammal to reduce or maintain intraocular pressure in the form of a mixture with an ophthalmically acceptable carrier. Any suitable, e.g., conventional, ophthalmically acceptable carrier may be employed. Such a carrier is ophthalmically acceptable if it has substantially no long term or permanent detrimental effect on the eye to which it is administered. Examples of ophthalmically acceptable carriers include water, in particular distilled water, saline and the like aqueous media. The present compounds are preferably administered to the eye as a liquid mixture with the carrier. The compounds are more preferably soluble in the carrier so that the compounds are administered to the eye in the form of a solution.

When an ophthalmically acceptable carrier is employed, it is preferred that the mixture contain one or more of the present compounds in an amount in the range of about 0.0001% to about 1%, more preferably about 0.05% to about 0.5%, w/v.

Any method of administering drugs directly to a mammalian eye may be employed to provide the present compound or compounds to the eye to be treated. By the term “administering directly” it is meant to exclude those general systemic drug administration modes, e.g., injection directly into the patients blood vessels, oral administration and the like, which result in the compound or compounds being systemically available. The primary effect on the mammal resulting from the direct administering of the present compound or compounds to the mammal's eye is preferably a reduction in intracocular pressure. More preferably, the present compound or compounds are applied topically to the eye or are injected directly into the eye. Particularly useful results are obtained when the compound or compounds are applied topically to the eye.

Topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose delivery, and fewer systemic side effects. An exemplary topical ophthalmic formulation is shown below in Table I. The abbreviation q.s. means a quantity sufficient to effect the result or to make volume.
TABLE I

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (% W/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present Quinoxaline Derivative</td>
<td>about 0.0001 to about 1.0</td>
</tr>
<tr>
<td>Preservative</td>
<td>0-0.10</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0-40</td>
</tr>
<tr>
<td>Tonicity Adjustor</td>
<td>1-10</td>
</tr>
<tr>
<td>Buffer</td>
<td>0.01-10</td>
</tr>
<tr>
<td>pH Adjustor</td>
<td>q.s. pH 4.5-7.5</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>as needed</td>
</tr>
<tr>
<td>Purified Water</td>
<td>as needed to make 100%</td>
</tr>
</tbody>
</table>

Various preservatives may be used in the ophthalmic preparation described in Table I above. Preferred preservatives include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate. Likewise, various preferred vehicles may be used in such ophthalmic preparation. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose, and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol, and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include but are not limited to, acetate buffers, citrate buffers, phosphate buffers, and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene.

Other excipient components which may be included in the exemplary ophthalmic preparation described in Table I are chelating agents which may be added as needed. The preferred chelating agent is edetate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Preparation of 1,2-dihydro-2,2-dimethyl-6-nitro-3-(4H)-quinoxalinone and 3,4-dihydro-3,3-dimethyl-6-nitro-2-(1H)-quinoxalinone

To a stirred solution of 4-nitro-1,2-phenylenediamine (Aldrich, 5.0 g, 32.6 mmol) and triethylamine (5.05 g, 50 mmol) in CH₂Cl₂ (50 ml) is added 2-bromo-2-methyl propionyl bromide (Aldrich 7.49 g, 32.6 mmol) dropwise. The mixture is stirred at room temperature until the starting material (4-nitro-1,2-phenylenediamine) is consumed. The reaction is quenched with aqueous NH₄Cl and the organic material is extracted with CH₂Cl₂. The organic extract is washed with H₂O (20 ml), dried over MgSO₄ and concentrated in vacuo. The residue is chromatographed on silica gel with hexanes: ethyl acetate elution to yield a mixture of bromo amide isomers. This mixture is dissolved in CH₂Cl₂ (30 ml) and treated with AgBF₄ - (Aldrich, 6.36 g, 32.6 mmol) at room temperature to effect cyclization. After the starting bromo amide isomers are consumed, the reaction is quenched with aqueous NH₄Cl and the organic material is extracted with CH₂Cl₂. The organic extract is washed with H₂O (10 ml), dried over MgSO₄ and concentrated in vacuo.

The residue is chromatographed on silica gel with hexanes: ethyl acetate elution to yield the title compounds in pure form. This chromatographing separates the title compounds and allows recovery of each of them individually.

EXAMPLE 2

Synthesis of 6-amino-1,2-dihydro-2,2-dimethyl-3-(4H)-quinoxalinone

A solution of 1,2-dihydro-2,2-dimethyl-6-nitro-3-(4H)-quinoxalinone (663 mg, 3 mmol) in CH₃OH (10 ml) is hydrogenated with 344.5 x 10³ Pa (50 psi) H₂ (g) at room temperature in the presence of a catalyst of
10% by weight palladium on charcoal (50 mg). After the starting material is consumed, the solution is filtered and concentrated in vacuo to yield 6-amino-1,2-dihydro-2,2-dimethyl-3-(4H)-quinoxalinone.

**EXAMPLE 3**

*Synthesis of 6-amino-5-bromo-1,2-dihydro-2,2-dimethyl-3-(4H)-quinoxalinone hydrobromide*

A solution of 6-amino-1,2-dihydro-2,2-dimethyl-3-(4H)-quinoxalinone (250 mg, 1.31 mmol) in glacial acetic acid (4 ml) is cooled using a water bath. Bromine (210 mg, 1.31 mmol) in acetic acid (0.25 ml) is added dropwise over a 5 minute period. The mixture is stirred at room temperature for 4 hours and the resulting precipitate is collected by vacuum filtration. The title compound is obtained in pure form after drying in vacuo.

**EXAMPLE 4**

*Synthesis of 2-imidazoline-2-sulfonic acid*

2-Imidazolidinethione (66.3 g, 650 mmol), Na₂MoO₄ (5 g, 227 mmol) and NaCl (15 g, 256 mmol) were added to 300 ml H₂O. Although some dissolution occurred, a solid residue remained in the liquid of the mixture. The mixture was cooled to -10°C using an immersion cooler. 500 ml of a 30% (w/v) aqueous H₂O₂ solution was placed in a jacketed controlled drip rate addition funnel and cooled to 0°C using an ice/H₂O bath. The aqueous H₂O₂ solution was added to the mixture at a rate of 60 drops/minute. The mixture was stirred for 16 hours at -10°C. During this time, the mixture changed from a white suspension to a dark blue solution to a light blue suspension. At the end of 16 hours, a solid was filtered from the suspension and dried in vacuo. No further purification was needed. 57.8 g (a yield of 52.3%) of the title compound as a white solid, which was characterized spectroscopically, was recovered. This solid was stable when stored in the dark at 0°C for at least 6 months.

**EXAMPLE 5**

*Synthesis of 5-bromo-1,2 dihydro-2,2-dimethyl-6-(2-imidazolin-2-ylamino)-3-(4H)-quinoxalinone*

A mixture of 6-amino-5-bromo-1,2-dihydro-2,2-dimethyl-3-(4H) - quinoxalinone hydrobromide (479 mg, 1 mmol) and 2-imidazoline-2-sulfonic acid (224 mg, 1.5 mmol) in isobutanol (5 ml) is heated at reflux until the starting hydrobromide material is consumed. The solvent is removed in vacuo and the residue chromatographed on silica gel with CHCl₃: CH₃OH saturated with NH₃ (g) elution to yield the title compound.

**EXAMPLE 6**

*Preparation of 5-bromo-2,2-dimethyl-6-(2-imidazolin-2-ylamino)-1,2,3,4-tetrahydroquinoline*

A suspension of 5-bromo-1,2-dihydro-2,2-dimethyl-6-(2-imidazolin-2-ylamino)-3-(4H)-quinoxalinone (150 mg, 0.45 mmol) and LiAlH₄ (17 mg, 0.45 mmol) in tetrahydrofuran (3 ml) is heated and maintained at a temperature of 50-80°C until the starting material is consumed. The mixture is cooled to 0°C, 2.3 drops of H₂O is added and the mixture is filtered. The solution is concentrated in vacuo to yield a residue which is chromatographed on silica gel with CHCl₃: CH₃OH saturated with NH₃ (g) elution to produce the title compound.

**EXAMPLE 7**

*Preparation of 5-bromo-3,4-dihydro-3,3-dimethyl-6-(2-imidazolin-2-ylamino)-2-(1H)-quinoxalinone*

By a series of reaction steps analogous to the steps described above in Examples 2 to 5, the title compound is prepared starting with 3,4-dihydro-3,3-dimethyl-6-nitro-2-(1H)-quinoxalinone in place of 1,2 dihydro-2,2-dimethyl-6-nitro-3-(4H)-quinoxalinone.
EXAMPLE 8

Preparation of 5-bromo-3,3-dimethyl-6-(2-imidazolin-2-ylamino)-1,2,3,4-tetrahydro-quinoxaline

Using the procedure illustrated in Example 6, the title compound is prepared starting with 5-bromo-3,4-dihydro-3,3-dimethyl-6-(2-imidazolin-2-ylamino)-2-(1H)-quinoxalinone in place of 5-bromo-1,2-dihydro-2,2-dimethyl-6-(2-imidazolin-2-ylamino)-3-(4H)-quinoxalinone.

EXAMPLES 9 TO 12

The four (4) quinoxaline derivatives produced in accordance with Examples 5 to 8 are tested to determine what effect, if any, these materials have on intraocular pressure.

Each of these materials is dissolved in distilled water at a concentration of 0.1% (w/v). Each of these solutions is administered topically and unilaterally to one eye of a drug-naive, unanesthetized New Zealand white rabbit in a single 50 micro liter drop. The contralateral eye received an equal volume of saline prior to determining the intraocular pressure after the mixture is administered. Also, approximately 10 micro liters of 0.5% (w/v) proparacaine (topical anesthetic) is applied to the corneas of each of the rabbits before determining intraocular pressure. As a control test, six (6) other drug-naive, unanesthetized New Zealand white rabbits are treated and tested as described above except that no quinoxaline derivative is included in the solutions administered to the eyes.

The intraocular pressure is determined in both eyes of each rabbit before and after the solution is administered. Such intraocular pressure determinations are made in the conventional manner using conventional equipment.

Results of these IOP determinations indicate that the four (4) quinoxaline derivatives produced in Examples 5 to 8 are effective to reduce intraocular pressure in the treated rabbit eye, i.e., the eye to which the active material was directly administered.

EXAMPLES 13 TO 16

The quinoxaline derivatives produced in Examples 5 to 8 are tested for activity using the following in vitro methods.

Rabbit Vas Deferens: Alpha 2 Adrenergic Receptors

New Zealand white rabbits (2-3 kg) are killed by CO₂ inhalation and the vasa deferentia is removed. The prostatic ends of the vasa deferentia (2-3 cm lengths) are mounted between platinum ring electrodes in 9 ml organ baths and bathed in Krebs bicarbonate solution of the following composition (millimolar): NaCl 118.0; KCl 4.7; CaCl₂ 2.5; MgSO₄ 1.2; KH₂PO₄ 1.2; glucose 11.0; NaHCO₃ 25.0; which solution is maintained at 35°C and bubbled with 95% O₂ and 5% CO₂. The initial tension of the vas deferens is 0.5 g.

The tissues are left to equilibrate for 30 minutes before stimulation is started. Vasa are then field stimulated (0.1 Hz, 2 ms pulse width at 90 mA) using a square wave stimulator (WPI A310 Accupulser with A385 stimulus). The contractions of the tissue are recorded isometrically using Grass FT03 force-displacement transducers and displayed on a Grass Model 7D polygraph. A cumulative concentration-response relationship is obtained for the quinoxaline derivative being tested with a 4 minute contact time at each concentration. Each of the quinoxaline derivatives of Examples 5 to 8 is effective to reduce the response height. Therefore, such compounds may be properly classified as Alpha 2 agonists.

EXAMPLES 17 TO 20

Each of the quinoxaline derivatives produced in Examples 5 to 8 is tested for renal and blood pressure effects using the following method.

Young male (20-24 weeks old) Sprague-Dawley rats are used. Under ketamine (80 mg/kg b.wt. i.m.) and pentobarbital (i.p. to effect) anesthesia, medical grade plastic tubes are implanted into the abdominal aorta and vena cava via the femoral vessels. In addition, a Silastic-covered stainless steel cannula is sewn in the urinary bladder. After the surgery, the rats are housed individually and are allowed free access to food and water until the day of the experiment.

For about 7 to 10 days before surgery and during recovery, the rats are accustomed to a restraining cage by placement in the cage for 2 to 3 hours every 2nd and 3rd day. The cage is designed for renal
clearance studies (a model G Restrainer sold by Braintree Scientific, Inc., Braintree, Massachusetts). The animals’ adjustment to the cage is judged by the stability of blood pressure and heart rate.

For an experiment, a rat is placed in the restraining cage, and the arterial line is connected to a Statham pressure transducer and a Beckman Dynograph R61 to monitor the mean arterial blood pressure, hereinafter referred to as MAP. The venous line is connected to an infusion pump system for infusion of replacement fluid. The quinoxaline derivative is administered intraduodenally by cannula. The bladder cannula was extended with a silastic tube to facilitate collection of urine in preweighed tubes. The volume of urine is measured gravimetrically. Body weight is recorded before and after the experiment.

Throughout the experiments, 0.9% NaCl containing 10% polyfructosan (Inutest) and 1% sodium PAH is infused at a rate of 20 microliters/min. An equilibration period of 60 minutes is followed by two consecutive 30 minute control clearance periods. Then, the quinoxaline derivative is administered for 90 minutes. Urine collection is resumed 10 minutes after the start of quinoxaline derivative administration. By this time the washout of the bladder cannula dead space (approximately 200 microliters) is completed. Three additional clearance measurements are made. Blood samples (150 microliters) are collected at the midpoint of urine collections. Plasma is separated and saved for analyses, and the cells are resuspended in saline and returned to the animals. Water and sodium loss is carefully replaced i.v. by a variable speed infusion pump.

Results of these tests indicate that the present quinoxaline derivatives produce renal effects, e.g., increased renal fluid flow. The effect on blood pressure of such derivatives is limited relative to such renal effects.

EXAMPLES 21 TO 24

Each of the quinoxaline derivative produced in Examples 5 to 8 is tested for anti-diarrheal effects and blood pressure effects using the following method.

Cecotomies are performed in unfasted rats in a conventional manner. The cecotomized rats are put into individual wire-bottomed cages placed over sheets of clean paper, and deprived of food and water for the duration of the assay. The MAP is monitored, as described in Examples 17 to 20, throughout the assay. Rats are given a 2 hour acclimatization period prior to the start of the assay in order to eliminate sporadic episodes of anxiety-induced defecation. During this period they are observed also for consistent occurrences of pelleted feces; an animal producing other than a pelleted stool is disqualified from the study.

Diarrhea is induced with oral administration of 16,16-dimethyl prostaglandin E2 (dmPGE2) in 3.5% EtOH. The quinoxaline derivative is administered by gavage after the onset of diarrheal episodes. The cage papers are removed and examined at 30 minute intervals for dmPGE2-induced diarrhea. Fecal output is recorded at each interval and fecal consistency is assigned a numerical score in each experimental group as follows: 1 = normal pelleted stool; 2 = soft-formed stools; 3 = water stool and/or diarrhea. The fecal output index (FOI) is defined as the summation of the number of defecation episodes and their ranked consistency score within an observation period.

Results of these tests indicate that the quinoxaline derivatives produced in Examples 5 to 8 provide substantial anti-diarrheal effects. Further, such anti-diarrheal effects are produced with no or relatively limited effects on blood pressure.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.
Claims for the following Contracting States: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound selected from the group consisting of those having the formula:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{R}_5 \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{R}_4 \\
\end{align*}
\]

and pharmaceutically acceptable acid addition salts thereof, wherein \( R_1 \) and \( R_4 \) are independently selected from the group consisting of \( H \) and alkyl radicals having 1 to 4 carbon atoms; the \( R_5 \) are each \( H \) or alkyl radicals having 1 to 4 carbon atoms or are, together, oxo; the \( R_3 \) are each \( H \) or alkyl radicals having 1 to 4 carbon atoms or are, together, oxo, provided that either both said \( R_5 \) or both \( R_3 \) are alkyl radicals; the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- positions of the quinoxaline nucleus; and \( R_6 \), \( R_5 \) and \( R_7 \) each is located in one of the remaining 5-, 6-, 7- or 8- positions of the quinoxaline nucleus and is independently selected from the group consisting of \( Cl, Br, H \) and alkyl radicals having 1 to 3 carbon atoms.

2. The compound of claim 1 wherein the 2-imidazolin-2-ylamino group is in the 6-position of the quinoxaline nucleus, \( R_5 \) is in the 5-position of the quinoxaline nucleus and is selected from the group consisting of \( Cl, Br \) and alkyl radicals containing 1 to 3 atoms, and \( R_6 \) and \( R_7 \) are both \( H \).

3. The compound of Claim 2 wherein each of \( R_1 \) and \( R_4 \) is \( H \).

4. The compound of Claim 2 or Claim 3 wherein said \( R_5 \) or said \( R_3 \) are methyl radicals.

5. The compound of Claim 2 or Claim 3 wherein said \( R_5 \) or said \( R_3 \) are \( H \).

6. The compound of Claim 2 or Claim 3 wherein said \( R_5 \) or said \( R_3 \) together is oxo.

7. The compound of any one of Claims 2 to 6 wherein \( R_5 \) is \( Br \).

8. The compound of Claim 1 having the formula:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{Br} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
9. The compound of Claim 1 having the formula:

10. The compound of Claim 1 having the formula:

11. The compound of Claim 1 having the formula:

12. A medication composition comprising:
   an amount of a compound effective to provide a desired therapeutic effect in a mammal to which
   said amount of said compound is administered, said compound being selected from the group of
   compounds claimed in Claim 1; and
   a carrier component combined with said compound in an amount effective to facilitate the
   administration of said amount of said compound to said mammal.

13. A medication composition comprising an effective amount of a compound as defined in any one of
    Claims 2 to 11.

14. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for use in altering
    the rate of fluid transport in the gastrointestinal tract of a mammal.

15. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for use in the
    maintenance of or reduction in the intraocular pressure in at least one eye of a mammal.

16. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for use in
    increasing the renal fluid flow in at least one kidney in a mammal.
Claims for the following Contracting States: ES, GR

1. A process for preparing a compound selected from the group consisting of those having the formula

and pharmaceutically acceptable acid addition salts thereof, wherein \( R_1 \) and \( R_4 \) are independently selected from the group consisting of \( H \) and alkyl radicals having 1 to 4 carbon atoms; the \( R_2 \) s are each \( H \) or alkyl radicals having 1 to 4 carbon atoms or are, together, oxo; the \( R_3 \) s are each \( H \) or alkyl radicals having 1 to 4 carbon atoms or are, together, oxo, provided that said \( R_2 \) s or said \( R_3 \) s are alkyl radicals; the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- positions of the quinoxaline nucleus; and \( R_5 \), \( R_6 \) and \( R_7 \) each is located in one of the remaining 5-, 6-, 7- or 8- positions of the quinoxaline nucleus and is independently selected from the group consisting of Cl, Br, H and alkyl radicals having 1 to 3 carbon atoms, characterized in that

(i) when the compound contains an oxo group, the hydrogenated product, produced by hydrogenating a nitro-substituted quinoxalinone and optionally halogenating the product is reacted with 2-imidazoline-2-sulfonic acid;
(ii) when the compound does not contain an oxo group, the oxo-containing quinoxaline product of (i) is reacted with an hydride reducing agent;
(iii) when in the compound \( R_1 \) and/or \( R_4 \) are alkyl the quinoxaline derivative having no substituents corresponding to \( R_1 \) and \( R_4 \) is reacted with a hydride reducing agent in the presence of an aldehyde or aldehydes selected on the basis of specific \( R_1 \) and/or \( R_4 \) alkyl group or group desired.

2. The process of Claim 1 for producing a compound as defined in Claim 1 wherein the 2-imidazolin-2-ylamino group is in the 6- position of the quinoxaline nucleus, \( R_5 \) is in the 5- position of the quinoxaline nucleus and is selected from the group consisting of Cl, Br and alkyl radicals containing 1 to 3 atoms, and \( R_6 \) and \( R_7 \) are both \( H \).

3. The process of Claim 2 wherein each of \( R_1 \) and \( R_4 \) is \( H \) in the compound.

4. The process of Claim 2 or Claim 3 wherein said \( R_2 \) s or said \( R_3 \) s are methyl radicals in the compound.

5. The process of Claim 2 or Claim 3 wherein said \( R_2 \) s or said \( R_3 \) s are \( H \) in the compound.

6. The process of Claim 2 or Claim 3 wherein said \( R_2 \) s or said \( R_3 \) s together is oxo in the compound.

7. The process of any one of Claims 2 to 6 wherein \( R_5 \) is \( Br \) in the compound.

8. The process of Claim 1 for producing a compound having the formula:
9. The process of Claim 1 for producing a compound having the formula:

10. The process of Claim 1 for producing a compound having the formula:

11. The process of Claim 1 for producing a compound having the formula:

Patentansprüche
Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung, ausgewählt aus der aus Verbindungen der Formel

und pharmaceutisch verträglichen Säureadditionssalzen davon bestehenden Gruppe, worin R₁ und R₆ unabhängig aus der aus H und Alkylresten mit 1 bis 4 Kohlenstoffatomen bestehenden Gruppe ausgewählt sind; die Reste R₂ jeweils H oder Alkylreste mit 1 bis 4 Kohlenstoffatomen bedeuten oder
zusammen Oxo bedeuten; die Reste R₅ jeweils H oder Alkylreste mit 1 bis 4 Kohlenstoffatomen bedeuten oder zusammen eine Oxogruppe bedeuten, mit der Maßgabe, daß entweder beide Reste R₅ oder beide Reste R₅ Alkylreste sind; die 2-Imidazolin-2-ylaminogruppe sich in einer beliebigen der Positionen 5, 6, 7 oder 8 des Chinoxalinkerns befindet; und sich die R₄, R₅ und R₇ sich jeweils in einer der verbleibenden Positionen 5, 6, 7 oder 8 des Chinoxalinkerns befinden und unabhängig aus der aus Cl, Br, H und Alkylresten mit 1 bis 3 Kohlenstoffatomen bestehenden Gruppe ausgewählt sind.


4. Verbindung nach Anspruch 2 oder 3, worin die Reste R₂ oder die Reste R₃ Methylreste bedeuten.

5. Verbindung nach Anspruch 2 oder 3, worin die Reste R₂ oder die Reste R₃ H bedeuten.

6. Verbindung nach Anspruch 2 oder 3, worin die Reste R₂ oder die Reste R₃ zusammen Oxo bedeuten.

7. Verbindung nach einem der Ansprüche 2 bis 6, worin R₆ Br bedeutet.

8. Verbindung nach Anspruch 1 mit der Formel:

```
\[
\begin{align*}
\text{HN} & \quad \text{NH} \\
\text{HN} & \quad \text{NH} \\
\text{N} & \quad \text{Br} \\
\text{H} & \quad \text{CH₃} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{CH₃} \\
\text{H} & \quad \text{CH₃}
\end{align*}
\]
```

9. Verbindung nach Anspruch 1 mit der Formel:

```
\[
\begin{align*}
\text{HN} & \quad \text{NH} \\
\text{HN} & \quad \text{NH} \\
\text{N} & \quad \text{Br} \\
\text{H} & \quad \text{CH₃} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{CH₃}
\end{align*}
\]
10. Verbindung nach Anspruch 1 mit der Formel:

![Chemical Structure 1](image1)

11. Verbindung nach Anspruch 1 mit der Formel:

![Chemical Structure 2](image2)

12. Arzneistoffzusammensetzung, umfassend:
   eine Menge einer Verbindung, die wirksam ist, um für eine gewünschte therapeutische Wirkung bei einem Säuger zu sorgen, dem die Menge an der Verbindung verabreicht wird, wobei die Verbindung aus der Gruppe von Verbindungen, die in Anspruch 1 beansprucht werden, ausgewählt ist; und
   eine Trägerkomponente, die mit der Verbindung in einer Menge kombiniert ist, die wirksam ist, um die Verabreichung der Menge der Verbindung an den Säuger zu erleichtern.

13. Arzneistoffzusammensetzung, umfassend eine wirksame Menge einer Verbindung, wie sie in einem der Ansprüche 2 bis 11 definiert ist.

14. Verwendung einer Verbindung, wie sie in Anspruch 1 beansprucht wird, für die Herstellung eines Arzneimittels zur Verwendung bei der Veränderung der Rate des Fluidtransports im Magen-Darm-Trakt eines Säugers.

15. Verwendung einer Verbindung, wie sie in Anspruch 1 beansprucht wird, für die Herstellung eines Arzneimittels zur Verwendung bei der Aufrechterhaltung oder Verringerung des Augeninnendrucks in mindestens einem Auge eines Säugers.

Patentansprüche für folgende Vertragsstaaten: ES, GR

1. Verfahren zur Herstellung einer Verbindung, ausgewählt aus der aus Verbindungen der Formel

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_6 \\
\text{R}_7 & \quad \text{R}_8 \\
\end{align*}
\]

und pharmazeutisch verträglichen Säureadditionssalzen davon bestehenden Gruppe, worin \( R_1 \) und \( R_4 \) unabhängig aus der aus H und Alkylresten mit 1 bis 4 Kohlenstoffatomen bestehenden Gruppe ausgewählt sind; die Reste \( R_2 \) jeweils H oder Alkylreste mit 1 bis 4 Kohlenstoffatomen bedeuten oder zusammen Oxo bedeuten; die Reste \( R_3 \) jeweils H oder Alkylreste mit 1 bis 4 Kohlenstoffatomen bedeuten oder zusammen eine Oxogruppe bedeuten, mit der Maßgabe, daß entweder beide Reste \( R_2 \) oder beide Reste \( R_3 \) Alkylreste sind; die 2-Imidazolin-2-ylaminogruppe sich in einer beliebigen der Positionen 5, 6, 7 oder 8 des Chinoxalinkerns befindet; und \( R_5 \), \( R_6 \), und \( R_7 \) sich jeweils in einer der verbleibenden Positionen 5, 6, 7 oder 8 des Chinoxalinkerns befinden und unabhängig aus der aus Cl, Br, H und Alkylresten mit 1 bis 3 Kohlenstoffatomen bestehenden Gruppe ausgewählt sind, dadurch gekennzeichnet, daß,

(i) sofern die Verbindung eine Oxogruppe enthält, das hydrierte Produkt, welches durch Hydrierung eines mit einer Nitrogruppe substituierten Chinoxalinons und wahlweise Halogenierung des Produktes hergestellt wurde, mit 2-Imidazolin-2-sulfonsäure umgesetzt wird;
(ii) sofern die Verbindung keine Oxogruppe enthält, das eine Oxo-Gruppe enthaltende Chinoxalinprodukt aus (i) mit einem Hydrid-Reduktionsmittel umgesetzt wird;
(iii) sofern \( R_1 \) und/oder \( R_4 \) in der Verbindung Alkylgruppen sind, das Chinoxalinderivat, welches keine \( R_1 \) und \( R_4 \) entsprechenden Substituenten enthält, mit einem Hydrid-Reduktionsmittel in Gegenwart eines Aldehyds oder Aldehyden, welche auf der Grundlage von spezifischen \( R_1 \)- und/oder \( R_4 \)-Alkylgruppen oder gewünschten Gruppen ausgewählt sind, umgesetzt wird.

2. Verfahren nach Anspruch 1 zur Herstellung einer in Anspruch 1 definierten Verbindung, worin sich die 2-Imidazolin-2-ylaminogruppe in der Position 6 des Chinoxalinkerns befindet, sich \( R_5 \) in der Position 5 des Chinoxalinkerns befindet und aus der aus Cl, Br und Alkylresten mit 1 bis 3 Kohlenstoffatomen bestehenden Gruppe ausgewählt ist und \( R_6 \) und \( R_7 \) beide H bedeuten.

3. Verfahren nach Anspruch 2, worin \( R_1 \) und \( R_4 \) in der Verbindung jeweils H bedeuten.

4. Verfahren nach Anspruch 2 oder 3, worin die Reste \( R_2 \) oder die Reste \( R_3 \) in der Verbindung Methylreste bedeuten.

5. Verfahren nach Anspruch 2 oder 3, worin die Reste \( R_2 \) oder die Reste \( R_3 \) in der Verbindung H bedeuten.

6. Verfahren nach Anspruch 2 oder 3, worin die Reste \( R_2 \) oder die Reste \( R_3 \) in der Verbindung zusammen Oxo bedeuten.

7. Verfahren nach einem der Ansprüche 2 bis 6, worin \( R_5 \) in der Verbindung Br bedeutet.
8. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung mit der Formel:

\[ \text{Chemical structure image} \]

9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung mit der Formel:

\[ \text{Chemical structure image} \]

10. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung mit der Formel:

\[ \text{Chemical structure image} \]

11. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung mit der Formel:

\[ \text{Chemical structure image} \]
Revendications

Revendications pour les États contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé choisi dans le groupe constitué par les composés répondant à la formule suivante:

\[ \text{Diagramme de la molécule} \]

et en leurs sels d'addition d'acide acceptables au plan pharmaceutique, formule dans laquelle les radicaux \( R_1 \) et \( R_4 \) sont indépendamment choisis dans le groupe constitué par H et les radicaux alcoyles ayant de 1 à 4 atomes de carbone; les radicaux \( R_2 \) sont chacun H ou des radicaux alcoyles ayant de 1 à 4 atomes de carbone ou forment, ensemble, un groupe oxo; les radicaux \( R_3 \) sont chacun H ou des radicaux alcoyles ayant de 1 à 4 atomes de carbone ou forment, ensemble, un groupe oxo, à la condition que soit les deux radicaux \( R_5 \), soit les deux radicaux \( R_6 \), soient des radicaux alcoyles; le groupe 2-imidazoline-2-ylamino peut occuper l'une des positions 5-, 6-, 7- ou 8- du noyau quinoxaline; et les radicaux \( R_6 \), \( R_7 \) et \( R_8 \) occupent chacun l'une des positions 5-, 6-, 7- ou 8- restantes du noyau quinoxaline et sont indépendamment choisis dans le groupe constitué par Cl, Br, H et les radicaux alcoyles ayant de 1 à 3 atomes de carbone.

2. Composé selon la revendication 1, dans lequel le groupe 2-imidazoline-2-ylamino occupe la position 6- du noyau quinoxaline le radical \( R_6 \) occupe la position 5- du noyau quinoxaline et est choisi dans le groupe constitué par Cl, Br et les radicaux alcoyles ayant de 1 à 3 atomes de carbone, et les radicaux \( R_6 \) et \( R_7 \) sont tous deux H.

3. Composé selon la revendication 2, dans lequel les radicaux \( R_1 \) et \( R_4 \) sont H.

4. Composé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont des radicaux méthyles.

5. Composé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont H.

6. Composé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont un groupe oxo.

7. Composé selon l'une des revendications 2 à 6, dans lequel le radical \( R_5 \) est Br.

8. Composé selon la revendication 1, de formule:

\[ \text{Diagramme de la molécule} \]
9. Composé selon la revendication 1, de formule:

10. Composé selon la revendication 1, de formule:

11. Composé selon la revendication 1, de formule:

12. Composition médicamenteuse comprenant:
   une quantité d'un composé efficace pour exercer un effet thérapeutique recherché chez un
   mammifère auquel ladite quantité dudit composé est administrée, ledit composé étant choisi dans le
   groupe de composés selon la revendication 1; et
   un constituant formant véhicule combiné avec ledit composé dans une quantité efficace pour
   faciliter l'administration de ladite quantité dudit composé audit mammifère.

13. Composition médicamenteuse comprenant une quantité efficace d'un composé défini dans l'une des
    revendications 2 à 11.

14. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament destiné à être
    utilisé pour modifier le taux du transfert liquidien dans le tractus gastro-intestinal d'un mammifère.

15. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament destiné à être
    utilisé pour maintenir ou réduire la pression intraoculaire dans au moins un œil d'un mammifère.

16. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament destiné à être
    utilisé pour augmenter le débit liquidien rénal dans au moins un rein d'un mammifère.
Revendications pour les États contractants suivants : ES, GR

1. Procédé de préparation d'un composé choisi dans le groupe constitué par les composés répondant à la formule suivante:

\[
\begin{align*}
&\text{H} \\
&\text{N} \equiv \text{N} \\
&\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
&\text{R}_4 \quad \text{R}_5 \\
&\text{R}_6 \\
&\text{H}
\end{align*}
\]

et en leurs sels d'addition d'acide acceptables au plan pharmaceutique, formule dans laquelle les radicaux \( R_1 \) et \( R_4 \) sont indépendamment choisis dans le groupe constitué par H et les radicaux alcoyles ayant de 1 à 4 atomes de carbone; les radicaux \( R_2 \) sont chacun H ou des radicaux alcoyles ayant de 1 à 4 atomes de carbone ou forment, ensemble, un groupe oxo; les radicaux \( R_3 \) sont chacun H ou des radicaux alcoyles ayant de 1 à 4 atomes de carbone ou forment, ensemble, un groupe oxo, à la condition que les deux radicaux \( R_2 \) ou les deux radicaux \( R_3 \) soient des radicaux alcoyles; le groupe 2-imidazoline-2-ylamino peut occuper l'une des positions 5-, 6-, 7- ou 8- du noyau quinoxaline; et les radicaux \( R_5 \), \( R_6 \) et \( R_7 \) occupent chacun l'une des positions 5-, 6-, 7- ou 8-restantes du noyau quinoxaline et sont indépendamment choisis dans le groupe constitué par Cl, Br, H et les radicaux alcoyles ayant de 1 à 3 atomes de carbone, caractérisé en ce que :

(i) lorsque le composé contient un groupe oxo, on fait réagir le produit hydrogéné, obtenu en hydrogénant une quinoxalinone nitro-substituée et éventuellement en halogénant le produit, avec un acide 2-imidazoline-2-sulfonique ;

(ii) lorsque le composé ne contient pas de groupe oxo, on fait réagir ce produit cité en (i) de quinoxaline contenant un oxo avec un agent hydrique réducteur ;

(iii) lorsque dans le composé les radicaux \( R_1 \) et/ou \( R_4 \) sont des radicaux alcoyles, on fait réagir le dérivé de quinaloxine n'ayant aucun substituant correspondant à \( R_1 \) et \( R_4 \) avec un agent hydrique réducteur en présence d'un aldéhyde ou d'aldéhydes choisis sur la base d'un groupe alcoyle spécifique \( R_1 \) et/ou \( R_4 \) ou d'un groupe désiré.

2. Procédé selon la revendication 1 pour produire un composé tel que défini à la revendication 1, dans lequel le groupe 2-imidazoline-2-ylamino occupe la position 6- du noyau quinoxaline, le radical \( R_5 \) occupe la position 5- du noyau quinoxaline et est choisi dans le groupe constitué par Cl, Br et les radicaux alcoyles ayant de 1 à 3 atomes de carbone, et les radicaux \( R_6 \) et \( R_7 \) sont tous deux H.

3. Procédé selon la revendication 2, dans lequel les radicaux \( R_1 \) et \( R_4 \) sont H dans le composé.

4. Procédé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont des radicaux méthyles dans le composé.

5. Procédé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont H dans le composé.

6. Procédé selon la revendication 2 ou la revendication 3, dans lequel les radicaux \( R_2 \) ou les radicaux \( R_3 \) sont un groupe oxo dans le composé.

7. Procédé selon l'une des revendications 2 à 6, dans lequel le radical \( R_5 \) est Br dans le composé.
8. Procédé selon la revendication 1, pour produire un composé de formule:

9. Procédé selon la revendication 1, pour obtenir un composé de formule:

10. Procédé selon la revendication 1, pour obtenir un composé de formule:

11. Procédé selon la revendication 1, pour produire un composé de formule: