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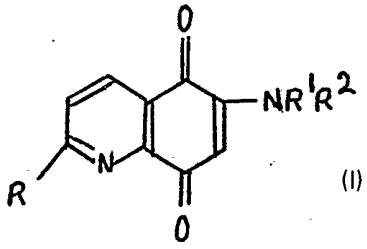
(71) Applicant
Eli Lilly and Company, (USA—Indiana), 307 East McCarty Street, Indianapolis, Indiana 46285, United States of America
(72) Inventors
Jerome Herbert Fleisch, Winston Stanley Marshall, George Joseph Cullinan
(74) Agent and/or address for service
T. R. Crowther, Erl Wood Manor, Windlesham, Surrey, GU20 6PH

(54) 6-Substituted-quinoline-5,8-quinones

(57) 6-Substituted-quinoline-5,8-quinones of the formula



(I)

wherein

R is hydrogen or C_1—C_3 alkyl, and R^1 and R^2 are independently hydrogen, C_1—C_6 alkyl, C_3—C_6 cycloalkyl, C_2—C_6 alkenyl, di-(C_1—C_6 alkyl)amino-(C_1—C_6 alkylene)-, tetrahydronaphthyl, or phenyl optionally substituted with a group R^3, where

R^3 is C_1—C_6 alkyl, except ortho-ethyl, trifluoromethyl, except para-trifluoromethyl, C_2—C_6 alkenyl, C_1—C_6 alkoxy, C_1—C_3 alkylthio, C_1—C_3 alkylcarbonyl, halo, nitro, or hydroxy, or

R^1 and R^2 together with the nitrogen atom to which they are attached form a morpholine or piperidine ring, are useful for therapy of immediate hypersensitivity reactions and conditions characterized by excessive release of leukotriene.

Most of the compounds I are novel.

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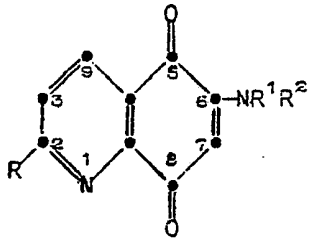
SPECIFICATION

6-Substituted-quinoline-5,8-quinones

This invention relates to 6-substituted-quinoline-5,8-quinones (also called 5,8-quinolinediones), which have been discovered to be useful for the therapy of immediate hypersensitivity reactions, such as asthma and conditions characterized by excessive release of slow-reacting substances or leukotrienes.

More specifically, a primary aspect of this invention resides in the discovery that a 6-substituted-quinoline-5,8-quinone of the formula (I)



wherein

R is hydrogen or C_1—C_3 alkyl; and

R^1 and R^2 are independently hydrogen, C_1—C_6 alkyl, C_3—C_6 cycloalkyl, C_2—C_6 alkenyl, di-(C_1—C_6 alkyl)amino-(C_1—C_6 alkylene), tetrahydronaphthyl, or phenyl optionally substituted with a group R^3 where

R^3 is C_1—C_6 alkyl except ortho ethyl, trifluoromethyl except para-trifluoromethyl, C_2—C_6 alkenyl, C_1—C_6 alkoxy C_1—C_3 alkylthio C_1—C_3 alkylcarbonyl halo nitro or hydroxy or

R^1 and R^2 together with the nitrogen atom to which they are attached form a morpholine or piperidine ring is useful to prevent excessive release of leukotrienes in mammals.

Compounds of formula (I) wherein R is hydrogen and (a) one of R^1 and R^2 is hydrogen and the other is phenyl, p-tolyl, p-chlorophenyl, n-hexyl, $(C_2H_5)_2N(CH_2)_3$—, $(C_2H_5)_2N(CH_2)_6$—, $(C_2H_5)_2N(CH_2)_3CH(CH_3)$—, or $(C_4H_9)_2N(CH_2)_3$—, or (b) R^1 and R^2 are both ethyl, or (c) one of R^1 and R^2 is methyl and the other is phenyl, or (d) R^1 and R^2 combine with the nitrogen to form piperidino have previously been reported in the literature. *J. Chem. Soc.,* 3919—24 (1953); *J. Chem. Soc.,* 570—74 (1954); *J. Org. Chem., 27* 3905—10 (1962); *J. Amer. Chem. Soc., 27,* 37—40 (1955). However, no utility for the reported compounds was demonstrated, and there was no recognition that the reported compounds might be useful in preventing excessive release of leukotrienes in mammals.

Thus, the invention provides novel compounds of formula (I) as defined above provided that if R and one of R^1 and R^2 are hydrogen, then the other of R^1 and R^2 is not phenyl, p-tolyl, p-chlorophenyl, n-hexyl, $(C_2H_5)_2N(CH_2)_3$—, $(C_2H_5)_2N(CH_2)_6$—, $(C_2H_5)_2N(CH_2)_3CH(CH_3)$—, or $(C_4H_9)_2N(CH_2)_3$—; and provided that if R is hydrogen and one of R^1 and R^2 is methyl, then the other of R^1 and R^2 is not phenyl and provided that if R is hydrogen and one of R^1 and R^2 is ethyl, then the other of R^1 and R^2 is not ethyl; and provided that if R is hydrogen, then R^1 and R^2 do not combine to form piperidino.

Preferred compounds are those wherein R^1 or R^4 is phenyl or substituted phenyl and R^2 or R^5 is hydrogen. Even more preferred are: 6-anilinoquinoline-5,8-quinone; and 6-(3-fluoroanilino)quinoline-5,8-quinone.

The following definitions refer to the various terms used throughout this disclosure. The term "C_1—C_6 alkyl" refers to the straight and branched saturated aliphatic radicals of one to six carbon atoms including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, neopentyl, hexyl, isohexyl (4-methylpentyl), sec-hexyl (1-methylpentyl), 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, and the like. The term "C_1—C_6 alkyl" includes within its definition the term "C_1—C_3 alkyl". The term "C_1—C_6 alkylene" refers to the straight and branched saturated aliphatic diradicals of one to six carbon atoms.

The term "C_3—C_6 cycloalkyl" refers to the saturated alicyclic rings of three to six carbon atoms, including cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "C_2—C_6 alkenyl" refers to unsaturated aliphatic radicals of two to six carbon atoms including ethylenyl, propenyl, butenyl, pentenyl, hexenyl, and the like.

The term "C_1—C_6 alkoxy" refers to the alkyl radicals of one to six carbon atoms attached to the remainder of the molecule by oxygen and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, and the like.

The term "C_1—C_3 alkylthio" refers to the alkyl radicals of one to three carbon atoms attached to the remainder of the molecule by sulfur and includes methylthio, ethylthio, propylthio, and the like.

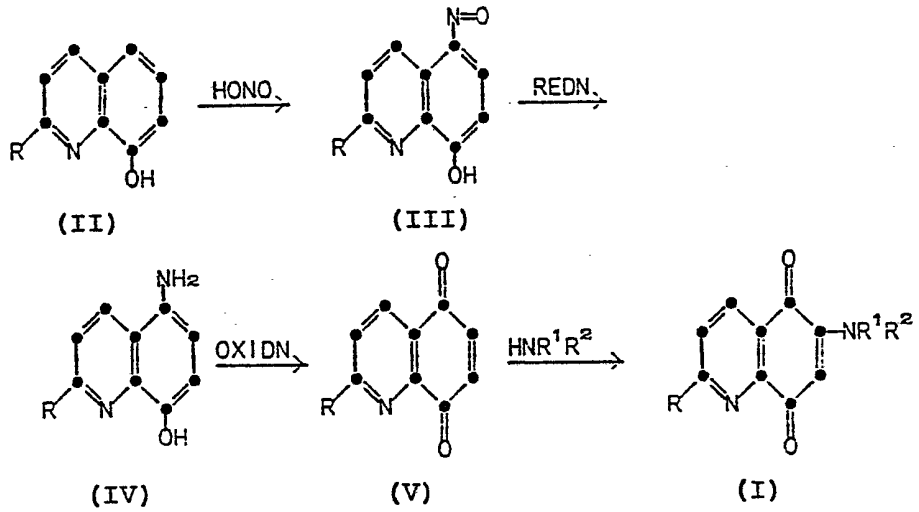
The term "C_1—C_3 alkylcarbonyl" refers to the alkyl radical of one to three carbon atoms attached to the remainder of the molecule by a carbonyl group (C=O) and includes methylcarbonyl, ethylcarbonyl, propylcarbonyl, and the like.

The term "halo" refers to chloro, bromo, fluoro, and iodo.

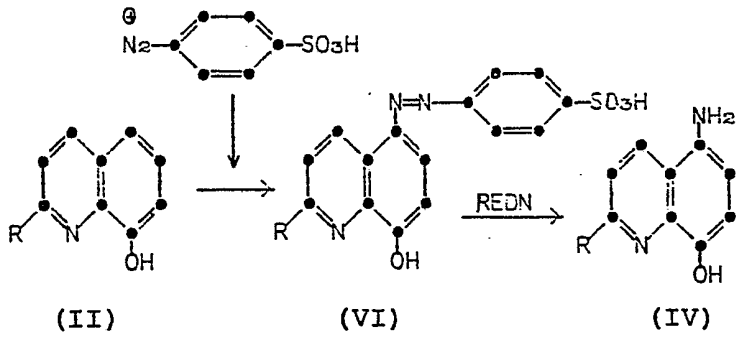
Preparation of compounds of formula (I)

The preparation of the quinoline-5,8-quinone compounds of formula (I) may follow one of the reaction schemes outlined below:

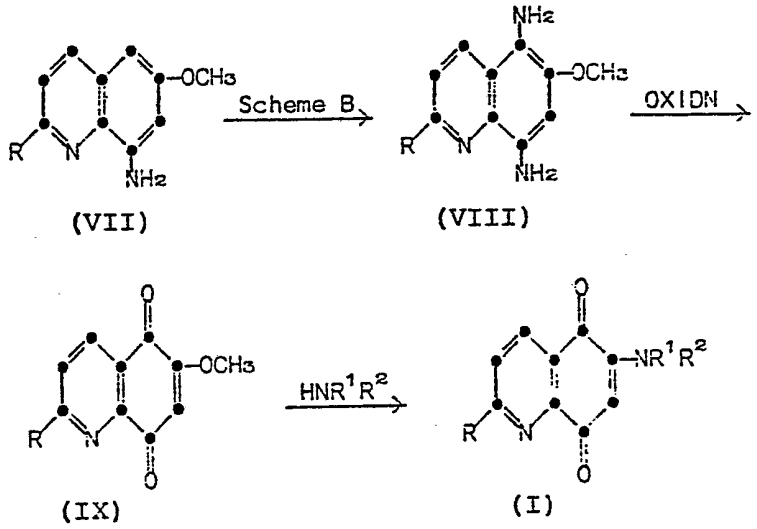
Scheme A



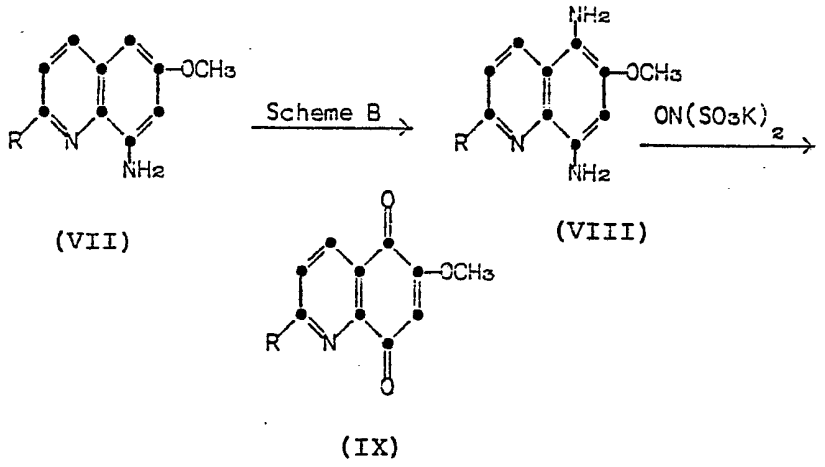
Scheme B



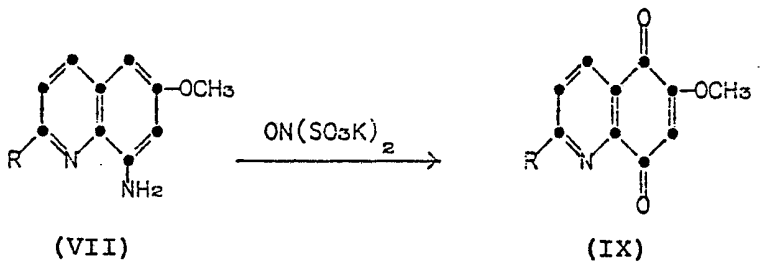
Scheme C



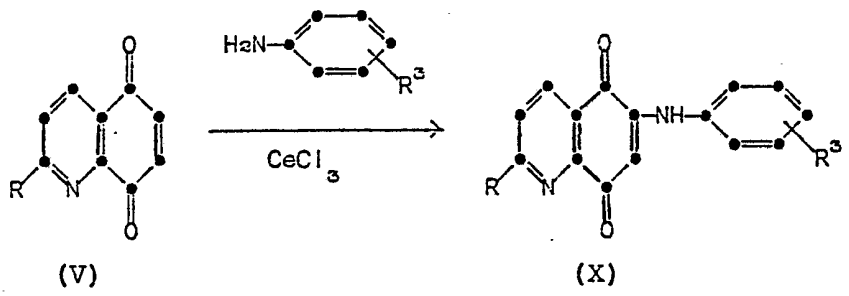
Scheme D



Scheme E



Scheme F



In Scheme A the 8-hydroxyquinoline (II) is reacted with nitrous acid to form 5-nitroso-8-hydroxyquinoline (III). The nitrous acid is generated *in situ* by the action of mineral acid, such as hydrochloric, sulfuric, and the like, on sodium nitrite usually under cold temperature conditions.

The nitroso compound (III) is then reduced by hydrogen gas using a metaly catalyst, such as Raney nickel, platinum, or palladium; by an acid and an appropriate metal, such as zinc, iron, or tin; by ammonium sulfide; by lithium aluminum hydride; by phenylhydrazine; and the like to form the amino-substituted compound (IV). The preferred reduction method is catalytic hydrogenation.

The hydroxy and amino groups of the amino-substituted compound (IV) are then oxidized by aqueous potassium or sodium dichromate; by chromic acid; by ferric chloride; by chromium (III) oxide in glacial acetic acid or pyridine; by permanganate; and the like, to form a quinoline-5,8-quinone (V). The preferred oxidizing agent is potassium dichromate.

To prepare a compound of formula (I), a solution of an amine of the formula HNR^1R^2, where R^1 and R^2 are as defined above, is added to the quinone (V) in the presence of an organic solvent. Such solvents as 1,2-dimethoxyethane, ethanol, and the like may be employed. The reaction is usually allowed to proceed at room temperature although elevated temperatures, up to the reflux temperature of the solvent, can be used. Additionally, the introduction of catalytic amounts of cerium chloride is

desirable in order to facilitate condensation. The reaction is worked up in the usual manner and the desired product may be purified by conventional means, such as crystallization or chromatography.

Scheme B illustrates an alternate method of preparing amino-substituted intermediates (IV). The 8-hydroxyquinoline (II) is coupled with a 4-diazobenzene-sulfonic acid salt (chloride, fluoborate) in mildly alkaline solution to form the azo compound (VI). The diazonium salt can be formed by dissolving the appropriate aniline in cold aqueous mineral acid and treating with sodium nitrite.

Sodium dithionite (hyposulfite) is then used to form the 5-amino compound (IV) from the azo compound in hot, aqueous mildly alkaline solution.

In Scheme C a 5,8-diamino-6-methoxyquinoline (VIII) is formed from the corresponding 8-amino-6-methoxyquinoline (VII) by following Scheme B. Then the diamino compound (VIII) is oxidized to form the corresponding diketone (IX), as described in Scheme A; followed by reaction with a primary or secondary amine of the formula HNR^1R^2 compound of formula (I). In particular, the 6-methoxyquinoline-5,8-quinone (IX) can be reacted with cerous chloride and the amine to form the 6-substituted amino-quinoline-5,8-quinone (I).

Scheme D illustrates an alternate method of preparing 6-methoxyquinoline-5,8-quinone intermediates of formula (IX). A diamino compound of formula (VIII) is formed from the corresponding amino compound by following Scheme B. Then the diamino compound is oxidized by Fremy's salt (potassium nitrosodisulfonate) to form the corresponding quinoline-5,8-quinone (IX).

In Scheme E the 8-amino-6-methoxyquinoline (VII) is oxidized to the corresponding diketone, 6-methoxyquinoline-5,8-quinone (IX), using Fremy's salt (potassium nitrosodisulfonate) without going through a diamino intermediate.

In Scheme F a 6-unsubstituted quinoline-5,8-quinone (V) is reacted with cerous chloride and a substituted aniline to form a 6-substituted anilinoquinoline-5,8-quinone, as described in the last step of Scheme C.

In particular, the anilinoquinoline-5,8-quinones can be made from the quinoline-5,8-quinone and corresponding aniline in a solvent, such as ethanol, and the like. The anilinoquinoline-5,8-quinone is then crystallized from the solvent, resulting in both the 6- and 7-substituted quinoline-5,8-quinone. Separation of the two isomers can be achieved by routine crystallization, and the desired 6-isomer isolated.

The preparation of some quinoline-5,8-quinones using the above preparation schemes is described in Long, R. and Schofield, K. "Some Properties and Reactions of Quinoline-5,8-quinones", *J. Chem. Soc.,* 3919—3924 (1953); Petrow, V. and Sturgeon, B. "Some Quinoline-5,8-quinones", *J. Chem. Soc.,* 570—574 (1954); Pratt, Y. T. and Drake, N. L. "Quinolinequinones. II. N-Substituted 6-Amino-5,8-quinolinequinones", *J. Amer. Chem. Soc., 77* 37—40 (1955); Pratt, Y. T. "Quinolinequinones. VI. Reactions with Aromatic Amines", *J. Org. Chem., 27,* 3905—3910 (1962); and Pratt, Y. T. and Drake, N. L. "Quinolinequinones, V. 6-Chloro- and 7-Chloro-5,8-quinolinequinones", *J. Amer. Chem. Soc., 82,* 1155—1161 (1960), which are incorporated by reference.

The preparation of the quinoline quinone compounds of this invention is described in the following examples. The examples are illustrative of the compounds embraced by the invention and of the methods commonly employed in their preparation, but are not to be construed as limiting the invention. All temperatures are in degrees Celsius.

Preparation 1
5,8-diamino-6-methoxyquinoline

Thirty-seven and one-half grams of *p*-sulfonylaniline sodium salt were dissolved in 150 ml of water and the resulting solution was added to 200 ml. of 1N hydrochloric acid. Then 150 ml. of an aqueous solution of 11.2 g. of sodium nitrite were added, forming a reddish solution, which contained *p*-diazobenzenesulfonic acid.

The reddish diazo solution was added to a solution of 25.0 g. of 8-amino-6-methoxyquinoline, 2 liter of glacial acetic acid, and 500 ml. of saturated aqueous sodium acetate, all of which had been cooled in an ice bath, while the reaction was stirred continuously with the diazo solution being added over about a 2 minute period. The stirring continued for about 1 minute after the diazo solution was added, then the reaction was allowed to sit in the ice bath for about one-half hour. A dark red precipitate was formed, which was filtered, and then washed with water.

The precipitate was then dissolved in a solution of 1 liter of water and 50 g. of sodium hydroxide and then heated to about 60° for about ten minutes. Slowly, 50 g. of sodium dithionite were added with stirring. After the addition, the reaction solution was kept at about 60° for about three hours. An orange precipitate was formed and the reaction was then allowed to cool to room temperature and sodium chloride was added. The orange solid, which was filtered and then dried, weighed 19 g (70% yield). It had a melting point of about 154.5—155.5° and the mass spectrum showed the expected molecular ion at m/e=189. The pKa was 5.08 using 66% aqueous dimethylformamide solution.

The NMR spectrum (deuterated chloroform) showed the following:

δ (ppm)=3.85 methoxy at 6-position
6.85 hydrogen at 7-position
7.3 hydrogen at 3-position
8.3 hydrogen at 4-position
8.55 hydrogen at 2-position

Preparation 2
2-methyl-5-amino-8-hydroxyquinoline

The preparation of 2-methyl-5-amino-8-hydroxyquinoline follows the procedure outlined in Preparation 1, except 15.9 g. of 2-methyl-8-hydroxyquinoline were used as the starting material. The product weighed 4.3 g (24.7% yield) and had a melting point of about 152—154°. The mass spectrum indicated the expected molecular ion at m/e=174. The pKa was 5.00, using 66% aqueous dimethylformamide solution and the apparent molecular weight was 188. In addition, the IR spectrum showed peaks at 3320 and 3400 cm^{-1}.

The NMR spectrum (deuterated chloroform) showed the following:

δ (ppm)=2.7 methyl at 2-position
6.6 hydrogen at 6-position
6.9 hydrogen at 7-position
7.3 hydrogen at 3-position
8.4 hydrogen at 4-position

The following elemental analysis was obtained:
Calculated for $C_{10}H_{10}N_2O$:

Theory:	C, 68.95;	H, 5.79;	N, 16.08
Found:	C, 68.57;	H, 5.60;	N, 15.97

Preparation 3
6-methoxyquinoline-5,8-quinone

Nineteen grams of 6-methoxy-5,8-diaminoquinoline were dissolved in 450 ml. of water and 10 ml. of concentrated sulfuric acid. The solution was cooled in an ice bath and then 50 ml. of potassium dichromate solution were added. (The dichromate solution was made by dissolving 50 g. of potassium dichromate in 500 ml. of water.) Forty ml. of concentrated sulfuric acid were added, followed by 190 ml. of the potassium dichromate solution, then 20 ml. of concentrated sulfuric acid, and finally 400 ml. of methylene chloride.

The reaction mixture was then stirred slowly and kept at about 25—30° throughout the reaction. After about 10 minutes, the methylene chloride was separated and 400 ml. of fresh methylene chloride were added.

The reaction was continued for another 20 minutes and again the methylene chloride was separated and a further 400 ml. of methylene chloride were added. After 40 minutes, the last methylene chloride fraction was separated. All the methylene chloride fractions were then combined and washed with an aqueous sodium chloride solution, then dried with anhydrous sodium sulfate, and evaporated to a tan amorphous powder. The powder was recrystallized in methanol to form yellow needles. The product weighed 4 g. (21% yield) and had a melting point of about 246—249°. The mass spectrum showed the expected molecular ion at m/e=189 and the IR spectrum indicated peaks at 1665 and 1685 cm^{-1}.

The following elemental analysis was obtained:
Calculated for $C_{10}H_7NO_3$:

Theory:	C, 63.49;	H, 3.73;	N, 7.40.
Found:	C, 63.27;	H, 3.93;	N, 7.13.

Preparation 4
2-methylquinoline-5,8-quinone

The preparation of 2-methylquinoline-5,8-quinone followed by the procedure of Preparation 3, except that 19 g of 2-methyl-5-amino-8-hydroxyquinoline prepared in Preparation 2 were used as the starting material. The product weighed 7 g. (37% yield) and the mass spectrum indicated the expected ion at m/e=173. The IR spectrum had peaks at 1660 and 1680 cm^{-1}.

The NMR spectrum (deuterated chloroform) shows the following:

δ (ppm)=2.8 methyl at 2-position
7.2 hydrogen at 6- and 7-position
7.6 hydrogen at 3-position
8.4 hydrogen at 4-position

The following elemental analysis was obtained:
Calculated for $C_{10}H_7NO_2$:

Theory:	C, 69.36;	H, 4.07;	N, 8.09.
Found:	C, 59.30;	H, 4.27;	N, 7.27.

Preparation 5
quinoline-5,8-quinone

The preparation of quinoline-5,8-quinone followed by the procedure of Preparation 3, except 60 g. of 5-amino-8-hydroxyquinoline were used as the starting material. The product weighed 30 g. (50% yield) and the mass spectrum indicated the expected molecular ion at m/e=159.

The following elemental analysis was obtained:
Calculated for $C_9H_5NO_2$:

Theory:	C, 67.93;	H, 3.17;	N, 8.80.
Found:	C, 68.07;	H, 3.02;	N, 8.85.

Preparation 6
6-methoxyquinoline-5,8-quinone

Eight and seven-tenths grams of 8-amino-6-methoxyquinoline were dissolved in 500 ml. of acetone and then 50 ml. of a 0.167 M of a potassium dihydrophosphate solution were added. Twenty-eight grams of Fremy's salt (potassium nitrosodisulfonate) were slowly added with stirring. The reaction was stirred at room temperature for several hours until the color changed from purple to red.

The acetone was removed from the reaction mixture *in vacuo*, then the resulting solution was extracted three times with chloroform. The chloroform extracts were combined, then dried with sodium sulfate and evaporated *in vacuo* to give a tan amorphous powder weighing 1 g. (11% yield). The mass spectrum showed the expected molecular ion at m/e=189.

Example 1
6-anilinoquinoline-5,8-quinone

Six grams of 6-methoxyquinoline-5,8-quinone were dissolved in 500 ml. of absolute ethanol and 9 g. of cerium chloride were added. After the reaction was stirred, 3.3 g. of aniline were added. The reaction mixture was refluxed for several hours, then it was stirred overnight at room temperature. The ethanol was evaporated to dryness and partitioned between chloroform and an aqueous sodium chloride solution. The chloroform layer was washed with an aqueous sodium chloride solution, dried with sodium sulfate, and then evaporated. The product was crystallized from absolute ethanol and weighed 3 g. (16% yield). It had a melting point of about 182—184° and the mass spectrum indicated the expected molecular ion at m/e=250.

The following elemental analysis was obtained:
Calculated for $C_{15}H_{10}N_2O_2$:

Theory:	C, 71.99;	H, 4.03;	N, 11.19.
Found:	C, 71.73;	H, 3.76;	N, 11.37.

Example 2
6-(4-methoxyanilino)quinoline-5,8-quinone

The preparation of 6-(4-methoxyanilino)quinoline-5,8-quinone followed the procedure in Example 1, except that 3.8 g. of 6-methoxyquinoline-5,8-quinone and 2.5 g of 4-methoxyaniline were used as the starting materials. The product had a melting point of about 212—213°. The mass spectrum indicated the expected molecular ion at m/e=280.

The NMR spectrum (deuterated chloroform) showed the following:

δ (ppm)=3.8 methoxy at 4-position of aniline ring
6.4 hydrogen at 7-position
6.9 hydrogen at 2-position of aniline ring
7.2 hydrogen at 3-position of aniline ring
7.5 hydrogen at 4-position
8.4 hydrogen at 3-position
8.8 hydrogen at 2-position

The following elemental analysis was obtained:
Calculated for $C_{16}H_{12}N_2O_3$:

Theory:	C, 68.56;	H, 4.32;	N, 9.99.
Found:	C, 68.79;	H, 4.54;	N, 9.70.

Example 3
6-(4-nitroanilino)quinoline-5,8-quinone

The preparation of 6-(4-nitroanilino)quinoline-5,8-quinone followed the procedure outlined in Example 1.

The product weighed 0.1 g. (3% yield) and the mass spectrum indicated the expected molecular ion at m/e=295.

The following elemental analysis was obtained:

Calculated for $C_{15}H_9N_3O_3$:

Theory: C, 61.02; H, 3.07; N, 14.23.

Found: C, 60.85; H, 3.36; N, 13.96.

Example 4

6-anilinoquinoline-5,8-quinone

Twenty and one-half grams of quinoline-5,8-quinone were dissolved in 500 ml. of absolute ethanol, then 13 g. of aniline were added, followed by the addition of 32 g. of cerium chloride. This reaction mixture was refluxed overnight. The resulting mixture had a brown-blue colour and was stirred and then left to cool to room temperature for about 26 hours.

Afterward the mixture was evaporated to dryness, boiled in ethyl acetate with some ethanol, and then washed with an aqueous sodium chloride solution. Upon drying with sodium sulfate, the reaction mixture was evaporated to dryness *in vacuo*. The product was crystallized from absolute ethanol and weighed 11 g. (34% yield).

The following elemental analysis was obtained:

Calculated for $C_{15}H_{10}N_2O_2$:

Theory: C, 71.99; H, 4.03; N, 11.19.

Found: C, 71.96; H, 4.03; N, 10.98.

The following compounds were prepared as in Example 4 and are shown in Table I:

Table I

Example no.	Compound	Mass spectrum m/e=	Elemental analysis					
			Theory			Found		
			C	H	N	C	H	N
5	2-methyl-6-anilinoquinoline-5,8-quinone	264	72.72	4.58	10.60	72.94	4.82	10.37
6	6-(1-amino-5,6,7,8-tetrahydro-naphthalene)quinoline-5,8-quinone	304	74.98	5.30	9.20	75.12	5.62	8.92
7	6-(4-hydroxyanilino)quinoline-5,8-quinone	266	67.67	3.79	10.52	67.09	4.22	10.41
8	6-cyclohexylaminoquinoline-5,8-quinone	256	70.29	6.29	10.93	70.06	6.12	10.69
9	6-(N-ethylanilino)quinoline-5,8-quinone	278	73.37	5.07	10.07	73.67	4.78	9.96
10	6-(4-fluoroanilino)quinoline-5,8-quinone	268	67.16	3.38	10.44	66.95	3.66	10.14
11	6-(2-fluoroanilino)quinoline-5,8-quinone	268 & 162	67.16	3.38	10.44	66.44	3.59	10.12
12	6-dimethylaminoethylamino-quinoline-5,8-quinone	245	63.66	6.16	17.13	63.46	6.09	16.91
13	6-(3-fluoroanilino)quinoline-5,8-quinone	268	67.16	3.38	10.44	66.90	3.20	10.14
14	6-(3-methylanilino)quinoline-5,8-quinone	264	72.72	4.58	10.60	72.85	4.81	10.47
15	6-(3-methoxyanilino)quinoline-5,8-quinone	280	68.56	4.32	9.99	69.22	4.56	10.26
16	6-(3-chloroanilino)quinoline-5,8-quinone	284 & 286	63.28	3.19	9.84	62.95	3.22	9.55
17	6-(3-bromoanilino)quinoline-5,8-quinone	328 & 330	54.74	2.76	8.51	54.92	2.78	8.50
18	6-(3-trifluoromethylanilino)quinoline-5,8-quinone	318	60.38	2.85	8.80	60.38	2.69	8.52
19	6-(3-acetylanilino)quinoline-5,8-quinone	292	69.86	4.14	9.58	70.08	4.25	9.32

The compounds of formula (I) are useful in treating any clinical condition characterized by excessive release of slow reacting substances of anaphylaxis (leukotrienes; SRS-A), which include immediate-type hypersensitivity reactions such as asthma. Evidence obtained over the past few years has shown the presence of leukotrienes in sputum of patients with chronic bronchitis (Turnbull *et al.*, Lancet II: 526, 1977) or cystic fibrosis (Cromwell *et al.* Lancet II: 164, 1981), suggesting a role for these substances in the pathology of these diseases. Therefore, the compounds described in this invention also should alleviate some of the symptoms of chronic bronchitis and cystic fibrosis by virtue of their ability to inhibit the release of leukotrienes.

The following test procedure and results demonstrate the utility of the compounds in inhibiting the release of leukotrienes, Male, Hartley guinea pigs, usually 1—2 weeks old were sensitized with respect to ovalbumin by intraperitoneal administration of 0.15 ml hyperimmune serum obtained from guinea pigs actively sensitized against ovalbumin. After 2 days or more, the animals were decapitated, lungs were excised and perfused through the pulmonary artery with Krebs'-bicarbonate solution of the following composition in mmoles/liter: KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 1.8; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; NaCl, 118.2; $NaHCO_3$, 24.8; and dextrose, 10.0. Poorly perfused and bloody areas were discarded. Normal lung was cut into 1 mm cubes with a McIlwain tissue chopper, washed with Krebs' solution and divided into 400 mg aliquots. The fragmented tissue was then incubated at 37°C. for 15 minutes in Krebs' solution containing indomethacin to optimize SRS-A release and an appropriate concentration of experimental drug. Antigen (ovalbumin) was then added to make a final concentration of 1×10^{-5} g/ml. Fifteen minutes later, the incubation medium was decanted and centrifuged at 3,000 g at 4°C. for 5 minutes. The supernatant solution was collected and assayed for SRS-A using a computerized bioassay that employs the isolated guinea pig ileum (Fleisch *et al., J. Pharmacol. Exp. Ther., 209* 238—243, 1979, which is incorporated by reference). Release of SRS-A in the presence of an experimental drug was compared to a control sample and the results expressed as percent inhibition of SRS-A release. These results are shown in Table II:

Table II — Inhibition of SRS-A release

Compound Example no.	*Percent inhibition in M concentration* 3×10^{-5}	1×10^{-5}	3×10^{-6}	1×10^{-6}
1, 4	86	79	54	28
2	NT*	32	NT	NT
3	NT	41	NT	NT
5	NT	55	NT	NT
6	NT	23	NT	NT
7	NT	58	NT	NT
8	NT	53	NT	0
9	NT	53	NT	NT
10	NT	39	NT	NT
11	NT	71	NT	0
12	NT	40	NT	NT
13	94	76	42, 80	13
14	NT	69	NT	NT
15	NT	72	NT	NT
16	NT	71	NT	NT
17	NT	45	NT	NT
18	NT	53	NT	NT
19	NT	NT	36	NT
6-(2-methylanilino)-quinoline-5,8-quinone	80	NT	17	NT
6-(2-methoxyanilino)-quinoline-5,8-quinone	38	NT	0	NT
6-(4-methoxyanilino)-quinoline-5,8-quinone	NT	32	NT	NT
6-(2-chloroanilino)-quinoline-5,8-quinone	78	NT	23	24
6-(4-chloroanilino)-quinoline-5,8-quinone	68	23	NT	NT
6-(2-trifluoromethylanilino)-quinoline-5,8-quinone	NT	52	NT	NT
6-(3-methylthioanilino)-quinoline-5,8-quinone	55	NT	16	NT
6-(N-methylanilino)-quinoline-5,8-quinone	NT	80	27	16
6-(N-propylanilino)-quinoline-5,8-quinone	39	28	NT	NT
6-[N-(2-propenyl)anilino]-quinoline-5,8-quinone	NT	41	NT	NT
6-methylaminoquinoline-5,8-quinone	51	28	NT	NT
6-isopropylamino-quinoline-5,8-quinone	28	NT	NT	NT
6-cyclopropylamino-quinoline-5,8-quinone	48	NT	NT	NT
6-(2-propenyl)aminoquinoline-5,8-quinone	NT	53	NT	NT
6-methylpropylamino-quinoline-5,8-quinone	61	NT	NT	NT
6-piperidinylquinoline-5,8-quinone	NT	68	NT	NT
6-morpholinylquinoline-5,8-quinone	63	28	NT	NT

*NT—Not Tested

Accordingly, the invention provides a method of treating an animal, including a human, suffering from or susceptible to any condition characterized by an excessive release of leukotrienes, which comprises administering to said animal a therapeutically-effective amount of a compound of formula (I) as defined above.

Also provided is a method of treating an animal, including a human, suffering from or susceptible to an immediate hypersensitivity reaction of the type represented by asthma, which comprises administering to said animal a therapeutically-effective amount of a compound of formula (I) as defined above.

The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g. by injection, and by continuous or discontinuous intra-arterial infusion. These formulations can be in the form of, for example, tablets, lozenges, sub-lingual tablets, sachets, cachets, elixirs, suspensions, aerosols, and ointments, containing an appropriate amount of the active compound in a suitable base. In addition, they can be soft and hard gelatin capsules, suppositories, injection solutions and suspensions in physiologically acceptable media, or sterile packaged powders adsorbed onto a support material for making injection solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from 5 to 500 mg (from 5.0 to 50 mg in the case of parenteral administration, from 5.0 to 50 mg in the case of inhalation and from 25 to 500 mg in the case of oral or rectal administration) of a compound of formula (I). Dosages of from 0.5 to 300 mg/kg per day, preferably 0.5 to 20 mg/kg of active ingredient may be administered, although it will, of course, readily be understood that the amount of the compound or compounds of formula (I) actually to be administered will be determined by a physician, in the light of all the relevant circumstances, including the condition to be treated, the choice of compound to be administered, and the choice of route of administration. Therefore, the above preferred dosage range is not intended to limit the scope of the present invention.

In this specification, the expression "dosage unit form" is used as meaning a physically discrete unit containing an individual quantity of the active ingredient, generally in admixture with a pharmaceutical diluent therefore, or otherwise in association with a pharmaceutical carrier, the quantity of the active ingredient being such that one or more units are normally required for a single therapeutic administration or that, in the case of severable units such as scored tablets, at least one fraction such as a half or a quarter of a severable unit is required for a single therapeutic administration.

The formulations of the present invention normally will consist of at least one compound of formula (I) mixed with a carrier; or diluted by a carrier or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container; or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid, or liquid material, which serves as a vehicle, excipient, or medium for the active therapeutic substance.

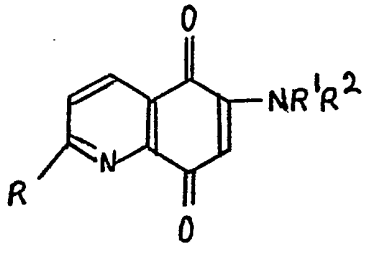
Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup U.S.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate, and oleyl alcohol. Propellants can be trichloromonofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, and the like. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed, for instance, aluminum, magnesium, or calcium stearates; talc; or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, suspensions, aerosols, injectible solutions, creams, and ointments. The most preferred forms are those used for inhalation application, such as suspensions, aerosols, and the like. Especially preferred is an aerosol formulation for inhalation application.

Thus, according to a further aspect of the present invention there is provided a pharmaceutical formulation which comprises as the active ingredient a therapeutically-effective amount of a compound of formula (I) as defined above, associated with a pharmaceutically-acceptable carrier therefor.

Claims

1. A compound of formula (I)



wherein

R is hydrogen or C_1—C_3 alkyl; and

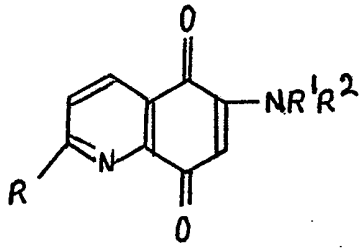
R^1 and R^2 are independently hydrogen, C_1—C_6 alkyl, C_3—C_6 cycloalkyl, C_2—C_6 alkenyl, di-(C_1—C_6 alkyl)amino-(C_1—C_6 alkylene)-, tetrahydronaphthyl, or phenyl optionally substituted with a group R^3, where

R^3 is C_1—C_6 alkyl, except orthoethyl, trifluoromethyl, except para-trifluoromethyl, C_2—C_6 alkenyl, C_1—C_6 alkoxy, C_1—C_3 alkylthio, C_1—C_3 alkylcarbonyl, halo, nitro, or hydroxy, or

R^1 and R^2 together with the nitrogen atom to which they are attached form a morpholine or piperidine ring, for use as a pharmaceutical agent to inhibit release of leukotriene.

2. A compound of formula (I) as claimed in claim 1 for use in treatment or prevention of immediate hypersensitivity reaction.

3. A compound of formula (I)



wherein

R is hydrogen or C_1—C_3 alkyl; and

R^1 and R^2 are independently hydrogen, C_1—C_6 alkyl, C_3—C_6 cycloalkyl, C_2—C_6 alkenyl, di-(C_1—C_6 alkyl)amino-(C_1—C_6 alkylene), tetrahydronaphthyl, or phenyl optionally substituted with a group R^3, where

R^3 is C_1—C_6 alkyl, except orthoethyl, trifluoromethyl, except para-trifluoromethyl, C_2—C_6 alkenyl, C_1—C_6 alkoxy, C_1—C_3 alkylthio, C_1—C_3 alkylcarbonyl, halo, nitro, or hydroxy, or

R^1 and R^2 together with the nitrogen atom to which they are attached form a morpholine or piperidine ring,

provided that if R and one of R^1 and R^2 are hydrogen, then the other of R^1 and R^2 is not phenyl, p-tolyl, p-chlorophenyl, n-hexyl, $(C_2H_5)_2N(CH_2)_3$—, $(C_2H_5)_2N(CH_2)_6$—, $(C_2H_5)_2N(CH_2)_3CH(CH_3)$—, or $(C_4H_9)_2N(CH_2)_3$—, and

provided that if R is hydrogen and one of R^1 and R^2 is methyl, then the other of R^1 and R^2 is not phenyl, and

provided that if R is hydrogen and one of R^1 and R^2 is ethyl, then the other of R^1 and R^2 is not ethyl, and provided that if R is hydrogen then R^1 and R^2 do not combine to form piperidino.

4. A compound of Formula (I) as claimed in claim 2 wherein R^1 is phenyl substituted by a group R^3 and R^2 is hydrogen.

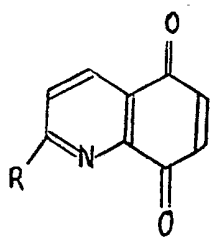
5. 6-(3-Fluoroanilino)quinoline-5,8-quinone.

6. A compound of formula (I) as claimed in any one of claims 3—5 for use as a pharmaceutical to inhibit release of leukotriene.

7. A compound of formula (I) as claimed in any one of claims 3—5 for use in treatment or prevention of immediate hypersensitivity reaction.

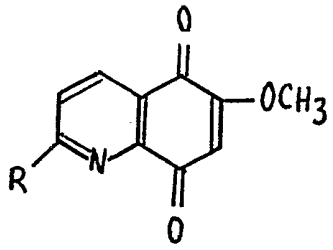
8. A process for preparing a compound of formula (I) as defined in any one of claims 3—5 which comprises

(A) reacting a compound of formula (V)



with an amine of formula HNR^1R^2 in a nonreactive organic solvent, or

(B) reacting a compound of formula (IX)



with cerous chloride and an amine of formula HNR^1R^2.

9. A pharmaceutical formulation which comprises as an active ingredient a compound of formula (I) as claimed in any one of claims 1—7 associated with one or more physiologically-acceptable carriers or vehicles therefor.

10. A compound of formula I as claimed in claim 3 substantially as hereinbefore described with reference to any one of the examples.

11. A process of preparing a compound of formula I as claimed in claim 8 substantially as hereinbefore described with reference to any one of the examples.

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