

PATENT SPECIFICATION

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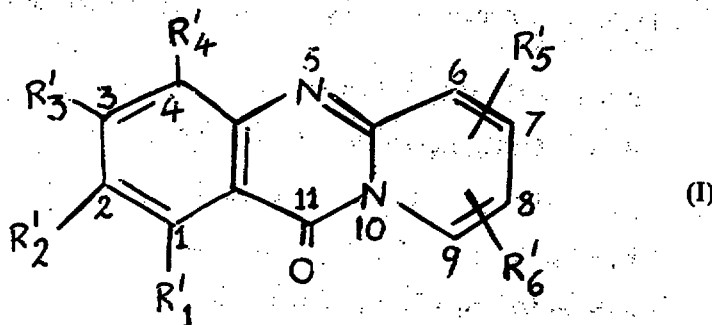


(54) 11-OXO-11(1H)-PYRIDO[2,1-b]QUINAZOLINES

(71) We, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey 07950, United States of America, a Corporation organised under the laws of the State of Delaware, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with 8 - (1H - tetrazol - 5 - yl) - 1H - pyridyl[2,1-b]quinazolin - 11 - ones and with the preparation thereof.

In our British Patent Specification No. 1,512,299, there are described and claimed compounds of the general formula:—



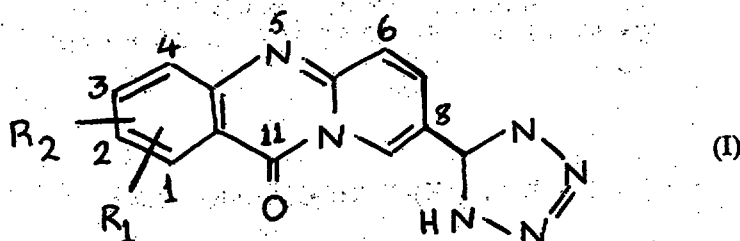
wherein R[']₁, R[']₂, R[']₃ and R[']₄, which may be the same or different, are hydrogen or halogen atoms or cyano, alkoxy, alkyl, alkenyl, aminoalkoxy, hydroxyalkoxy, hydroxyl, aralkyloxy, trifluoromethyl, nitro, amino, monoalkylamino, dialkylamino, aralkylamino, acylamino, sulphonylamino, carboxy, carboalkoxy, carbamoyl, N-substituted carbamoyl, methylsulphonyl, methylsulfonyl, arylsulphonyl, arylsulfonyl, sulphamoyl, sulphonic acid, acrylic acid, oxycetic acid, tetrazolyl, N-tetrazolylcarbamoyl or tetrazolyl ethylene radicals or wherein two substituents R[']₁—R[']₄ represent an alkylenedioxy radical, R[']₅ is a hydrogen atom or a hydroxyl, hydroxyalkyl, hydroxyalkoxy, carboxy, carboalkoxy, carbamoyl, N-substituted carbamoyl, tetrazolyl, N-tetrazolylcarbamoyl, tetrazolyethylene, sulphamoyl sulphonic acid, acrylic acid, cyano, oxycetic acid or oxymethyltetrazolyl radical in the 6-, 7-, 8- or 9-position of the pyrido ring and R[']₆ is a hydrogen atom or a hydroxyl, alkoxy or alkyl radical; with the proviso that R[']₁, R[']₂, R[']₃, R[']₅ and R[']₆ cannot all be hydrogen atoms, with the proviso that when R[']₁, R[']₂, R[']₃ and R[']₄ are all hydrogen atoms, then R[']₅ is other than a carboxy group in the 6-position, with the proviso that when one of R[']₁, R[']₂, R[']₃ and R[']₄ is a nitro group, then the other symbols R[']₁, R[']₂, R[']₃ and R[']₄ and R[']₅ and R[']₆ cannot all be hydrogen atoms; with the proviso that when one of R[']₁, R[']₂, R[']₃ and R[']₄ is a bromine atom, then the other symbols R[']₁, R[']₂, R[']₃ and R[']₄ and R[']₅ and R[']₆ cannot all be hydrogen atoms, and with the proviso that when three of R[']₁, R[']₂, R[']₃ and R[']₄

14

are all chlorine atoms, then the other symbols R'_1 , R'_2 , R'_3 and R'_4 and R'_5 and R'_6 cannot all be hydrogen atoms; and the pharmaceutically acceptable salts thereof with acids and bases. These compounds are useful for the management of allergic conditions, such as bronchial asthma.

We have now found a small group of compounds which fall within the ambit of general formula (I) but which are not exemplified therein and which are more effective for the management of allergic conditions, such as bronchial asthma. These compounds are characterised by containing a tetrazol-5-yl radical in the 8-position.

Thus, according to the present invention, there are provided compounds of the general formula:—



wherein R_1 and R_2 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl groups or alkyl or alkoxy radicals or R_1 and R_2 together can represent a methylenedioxy radical when they are attached to adjacent positions of the ring system; and the pharmaceutically-acceptable salts thereof with acids and bases.

In the above definitions of R_1 and R_2 , the alkyl radical and the alkyl portion in the alkoxy radical contain up to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl radicals. The term "halogen" includes all the four members, i.e. fluorine, chlorine, bromine and iodine.

The preferred compounds of the present invention falling within the above generic description are:

$R_1 = R_2 = H$ and $R_3 = 5$ -tetrazolyl

$R_1 = 2-OCH_3$, $R_2 = H$, $R_3 = 5$ -tetrazolyl

$R_1 = 2-CH_3$, $R_2 = H$, $R_3 = 5$ -tetrazolyl

$R_1 + R_2 = 2,3$ -di- OCH_3 , $R_3 = 5$ -tetrazolyl

$R_1 = 2-OH$, $R_2 = H$, $R_3 = 5$ -tetrazolyl

The compounds of the present invention have been found to reduce allergic responses to antigen challenge by inhibiting antibody-antigen reactions in mammals, such as rats. When tested in accordance with the procedure of Herzig (Immunopharmacology, M.E. Rosenthale and H.C. Mansmann, Eds., John Wiley and Son, N.Y., 1975), these compounds inhibit allergic responses or passive cutaneous anaphylaxis (PCA) in the rat when administered orally, parenterally or by aerosol at a dose of 0.001 — 20 mg/kg. Accordingly, these compounds are indicated in the management of allergic conditions, such as bronchial asthma.

Thus, according to the present invention, there are provided pharmaceutical compositions comprising at least one of the compounds according to the present invention, in admixture with a solid or liquid pharmaceutical diluent or carrier.

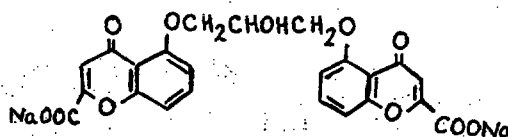
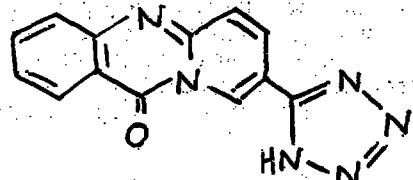
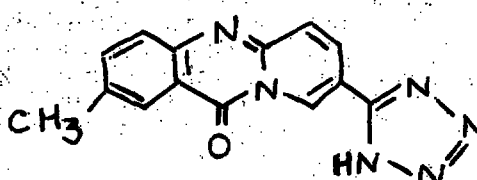
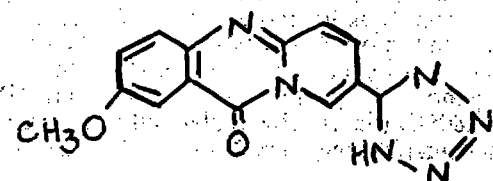
Generally speaking, in an adult human, a dose of 0.001 — 20 mg./kg. orally, parenterally or by aerosol administration 1 to 3 times daily is suggested for the relief of bronchial asthma. As with anti-allergy treatment, the dose is to be adjusted for individual needs but is within the above range.

The compounds of the present invention are more potent and orally effective than previously known compounds, such as disodium cromoglycate.

Thus, for example, disodium cromoglycate in the above-mentioned PCA test was found to be orally inactive, whereas the compounds of the present invention were found to be orally active. Parenterally, the compounds of the present invention were also found to be more potent than disodium cromoglycate.

The results of comparative tests between disodium cromoglycate and three of the new compounds of the present invention are shown in the following Table:—

TABLE

test compound	ED ₅₀ -PCA (rat)	
	iv	po
 (disodium cromoglycate)	1-2 mg/kg	inactive
	0.5 mg/kg	0.5 mg/kg
	0.04 mg/kg	—
	0.005 mg/kg	0.05 mg/kg

According to the present invention, the compounds (I) can be prepared as follows:

An appropriately substituted anthranilic acid is condensed with one equivalent of 6-chloronicotinamide in an acid to give the corresponding substituted 8-carbamoyl - pyrido[2,1-b]quinazolin - 11 - one, which is dehydrated to give the corresponding nitrile derivative, using for example *p*-toluenesulphonyl chloride in pyridine and dimethyl formamide, the desired tetrazolyl product being obtained from the nitrile by using sodium azide, ammonium chloride and dimethylformamide.

The following gives a more detailed description of this three-stage process:

Substituted 8 - carbamoyl - 11 - oxo - 11(1H) - pyrido[2,1-b] - quinazolines.

A mixture of 1 — 2.5 parts of a substituted anthranilic acid, 1 part of 6-chloronicotinamide, 0.1 — 2 parts of a mineral acid, such as concentrated hydrochloric acid, and 20 parts of an alcohol, such as ethanol, is heated under reflux for 8 — 72

16

4

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4

hours. The reaction mixture is cooled and the product separates and is collected by filtration (70% yield). Purification is accomplished by recrystallisation from an appropriate solvent, such as pyridine.

Substituted 8 - cyano - 11 - oxo - 11(1H) - pyrido[2,1-b] - quinazolines.

A reaction mixture composed of 1 part of a 8 - carbamoyl - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline, 1 — 4 parts of *p*-toluenesulphonyl chloride, 5 — 20 parts of dimethylformamide and 20 — 100 parts of pyridine is heated at 75 — 130°C. for 8 — 64 hours. The product obtained as a precipitate after the reaction is poured on to 200 parts of ice/water and acidified with a mineral acid. The crude yield is 72%. A sample of analytical purity can be obtained by recrystallisation from an appropriate solvent, such as pyridine.

Substituted - 8 - (tetrazol - 5 - yl) - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazolines.

A mixture of 1 part of a substituted 8 - cyano - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline, 2 — 5 parts of sodium azide, 2 — 5 parts of ammonium chloride and 50 — 200 parts of dimethylformamide is heated for 6 — 64 hours at 80 — 130°C. The reaction mixture is cooled and poured on to 1000 parts of ice/water and acidified with a mineral acid, such as hydrochloric acid. The product is obtained as a precipitate and is collected by filtration (83% yield). Purification is accomplished by recrystallisation from an appropriate solvent, such as pyridine.

The salts of the compounds (I) can be prepared, for example, by reacting with an appropriate base, such as sodium or potassium bicarbonate, or with an appropriate acid, such as hydrochloric, hydrobromic or sulphuric acid.

The following Example is given for the purpose of illustrating the present invention:—

Example 1.

a) 8 - Carbamoyl - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline

A mixture of 27.0 g (161 mM) 5 - methoxy - anthranilic acid, 25 g. (160 mM) 6 - chloronicotinamide and 500 ml. ethanol containing 15 ml. concentrated hydrochloric acid was heated under reflux for 24 hours. The reaction mixture was cooled to 0°C. and the resultant solid precipitate was filtered off to give 34.0 g. (69.5% of theory) of crude 8 - carbamoyl - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline hydrochloride salt. This compound was recrystallized twice from pyridine to give an analytical sample, m.p. 329 — 332°C. (dec.).

b) 8 - Cyano - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.

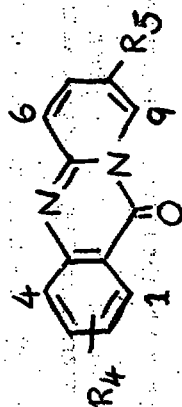
A solution of 1.2 litres pyridine, 300 ml. dimethylformamide, 7.46 g. (39.4 mM) *p*-toluenesulphonyl chloride and 7.45 g. (27.6 mM) 8 - carbamyl - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline was heated at 100°C. for 42 hours. The reaction mixture was cooled and poured into 4 litres ice/water and acidified to pH 1 with concentrated hydrochloric acid. The solid which formed was filtered off to give 5.0 g. (72.2% of theory) 8 - cyano - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline; m.p. 273 — 280°C. (dec.). The analytically pure nitrile was obtained after one recrystallisation from pyridine; m.p. 281 — 185°C. (dec.).

c) 2 - Methoxy - 8 - (tetrazol - 5 - yl) - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.

A mixture of 3.00 g. (12 mM) 8 - cyano - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline, 2.22 g. (34.2 mM) sodium azide, 1.83 g. (34.2 mM) ammonium chloride and 250 ml. dimethylformamide was heated at 115°C. for 20 hours. The reaction mixture was cooled, poured on to 1.5 litres of ice/water and acidified with concentrated hydrochloric acid. The solid which formed was filtered off to give 2.93 g. (83% of theory) 2 - methoxy - 8 - (tetrazol - 5 - yl) - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline; m.p. 279 — 299°C. (dec.). A sample of analytical purity was obtained by recrystallisation from pyridine; yield 2.25 g. (64% of theory); m.p. 302 — 304°C. (dec.).

Other compounds of the present invention can be prepared in an analogous manner. The physical characteristics of some of the compounds of the present invention are set out in the following Table, together with the physical characteristics of the corresponding carbamoyl and cyano intermediates.

TABLE



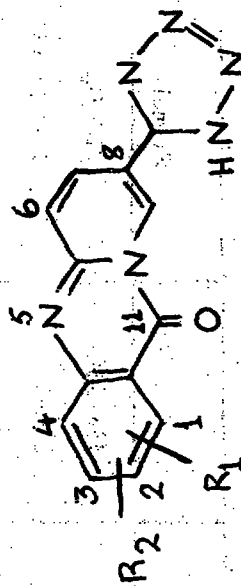
R ₄	R ₅	m.p. °C. (dec.)	Formula	Elemental Analysis	Solvent of recrystallisation
H	8-CONH ₂	338-344	C ₁₃ H ₉ N ₃ O ₂	CHN	pyridine
H	8-CN	249-251	C ₁₃ H ₇ N ₃ O _{1.1} /4H ₂ O	CHN	pyridine
H	8-(5-tetrazoly)	293-295	C ₁₃ H ₇ N ₆ O _{1.1} /4C ₂ H ₆ O	CHN	EtOH
2-CH ₃	8-CONH ₂	332-336	C ₁₄ H ₁₁ N ₃ O ₂	CHN	pyridine
2-CH ₃	8-CN	307-309	C ₁₄ H ₉ N ₃ O	CHN	pyridine
2-CH ₃	8-(5-tetrazoly)	284-286	C ₁₄ H ₉ N ₆ O ₂	CHN	pyridine
2-OCH ₃	8-CONH ₂	329-332	C ₁₄ H ₁₁ N ₃ O ₂	CHN	pyridine
2-OCH ₃	8-CN	281-285	C ₁₄ H ₉ N ₃ O ₂	CHN	pyridine
2-OCH ₃	8-(5-tetrazoly)	302-304	C ₁₄ H ₉ N ₆ O ₂	CHN	pyridine
3-OCH ₃	CN	273-275	C ₁₄ H ₉ N ₃ O ₂	CHN	pyridine
3-OCH ₃	8-(5-tetrazoly)	284-287	C ₁₄ H ₉ N ₆ O ₂	CHN	pyridine
2,3-di-OCH ₃	CONH ₂	313-318	C ₁₅ H ₁₃ N ₃ O _{4.1} /2H ₂ O	CHN	pyridine
2,3-di-OCH ₃	CN	309-312	(C ₁₅ H ₁₁ N ₃ O _{3.1} /2H ₂ O	CHN	pyridine

TABLE (Continued)

R ₄	R ₅	m.p. °C. (dec)	Formula	Elemental analysis	Solvent of Recrystallisation
2,3-di-OCH ₃	8-(5-tetrazolyl)	300-303	C ₁₄ H ₁₂ N ₆ O ₃	CHN	pyridine
2,3-methylenedioxy	CONH ₂	368-373	C ₁₄ H ₁₀ N ₆ O ₄	CHN	pyridine
2,3-methylenedioxy	CN	319-323	C ₁₄ H ₁₀ N ₆ O ₃	CHN	pyridine
2,3-methylenedioxy	8-(5-tetrazolyl)	310-313	C ₁₄ H ₁₀ N ₆ O ₃	CHN	pyridine

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



- 5 wherein R₁ and R₂, which can be the same or different are hydrogen or halogen atoms or hydroxyl groups or alkyl or alkyloxy radicals or R₁ and R₂ together represent a methylenedioxy radical when they are attached to adjacent positions of the ring system; and the pharmaceutically acceptable salts thereof with acids and bases.
- 10 2. 8 - (Tetrazol - 5 - yl) - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.
3. 8 - (Tetrazol - 5 - yl) - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.

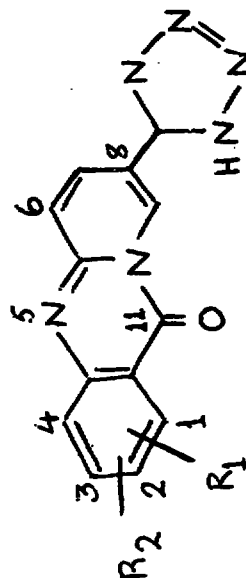


TABLE (Continued)

R ₁	R ₂	m.p. °C. (dec.)	Formula	Elemental analysis	Solvent of Recrystallisation
2,3-di-OCH ₃	8-(5-tetrazolyl)	300-303	C ₁₈ H ₁₂ N ₆ O ₃	CHN	pyridine
2,3-methylenedioxy	CONH ₂	368-373	C ₁₄ H ₈ N ₄ O ₄	CHN	pyridine
2,3-methylenedioxy	CN	319-323	C ₁₄ H ₈ N ₄ O ₃	CHN	pyridine
2,3-methylenedioxy	8-(5-tetrazolyl)	310-313	C ₁₄ H ₈ N ₆ O ₃	CHN	pyridine

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



- 5 wherein R₁ and R₂, which can be the same or different are hydrogen or halogen atoms or hydroxyl groups or alkyl or alkyloxy radicals or R₁ and R₂ together represent a methylenedioxy radical when they are attached to adjacent positions of the ring system; and the pharmaceutically acceptable salts thereof with acids and bases.
- 10 2. 8 - (Tetrazol - 5 - yl) - 2 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.
3. 8 - (Tetrazol - 5 - yl) - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.

191

7

1,592,867

7

4. 8 - (Tetrazol - 5 - yl) - 2 - methyl - 11 - oxo - 11(1H) - pyrido[2,1-b]-quinazoline.
5. 8 - (Tetrazol - 5 - yl) - 3 - methoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]-quinazoline.
- 5 6. 8 - (Tetrazol - 5 - yl) - 2,3 - dimethoxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline. 5
7. 8 - (Tetrazol - 5 - yl) - 2,3 - methylenedioxy - 11 - oxo - 11(1H) - pyrido[2,1-b]quinazoline.
- 10 8. Process for the preparation of compounds of the general formula given in claim 1, wherein an appropriately substituted anthranilic acid is condensed with one equivalent of 6-chloronicotinamide in an acid to give the corresponding substituted 8 - carbamoyl - pyrido[2,1-b]quinazolin - 11 - one which is dehydrated to give the corresponding nitrile and this then reacted with sodium azide, ammonium chloride and dimethylformamide to give the corresponding tetrazolyl. 10
- 15 9. Process according to claim 8, wherein the product obtained is reacted with an acid or a base to give a corresponding salt. 15
- 10 10. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified. 20
11. Compounds according to claim 1, whenever prepared by the process according to any one of claims 8 to 10. 20
12. Pharmaceutical compositions, comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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