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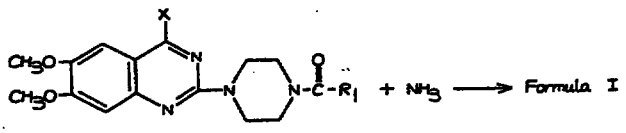
(54) 2-PIPERAZINYL-6,7-DIMETHOXYQUINAZOLINES

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having offices located at 345 Park Avenue, New York, New York 10022, 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:–

This invention provides quinazoline compounds and pharmaceutically acceptable acid addition salts thereof having pharmacological properties making them particularly useful as antihypertensive agents. The quinazoline class of compounds of the present invention structurally resemble the 2,4,6,7-tetrasubstituted quinazoline antihypertensive agents disclosed in U.S. Patent No. 3,511,836. The compound "2-[4-(2-furoyl)-1-piperazin-1-yl]-4-amino-6,7-dimethoxy-quinazoline", known as prazosin, is representative of the quinazolines of the '836 Patent and has been studied in the clinic. Although prazosin is apparently an effective antihypertensive agent, it is not altogether free from *alpha*-adrenoreceptor blocking activity or from undesirable side effects such as postural dizziness and orthostatic hypotension; N. E. Pitts, Postgraduate Medicine, Prazosin, pp. 117–127 (November, 1975).

In general, the compounds of the present invention are substantially more potent than prazosin as antihypertensives but exhibit appreciably less *alpha*-adrenoreceptor blocking activity. Also, compared to prazosin, the compounds of the present invention are more potent phosphodiesterase inhibitors and exhibit greater selectivity for the enzyme operative on the cyclic guanosine monophosphate (cyclic GMP) substrate.

This invention is concerned with new quinazoline compounds, a process for their preparation and pharmaceutical compositions thereof. The quinazolines, possess valuable pharmalogic properties and another aspect of this invention relates to an antihypertensive process utilizing the new compounds. More particularly, the invention is especially concerned with 2-piperazinyl-6,7-dimethoxyquinazolines characterized by Formula I



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Formula I

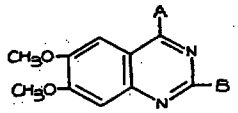
and pharmaceutically acceptable acid addition salts thereof wherein R is amino or hydrazino; and R_1 is cycloalkyl, or methylcycloalkyl, each having from 3 to 8 ring carbon atoms inclusive and cycloakenyl having 4 to 8 carbon atoms inclusive.

It is to be understood that the term "cycloalkyl" as used herein includes cycloalkyl radicals containing 3 to 8 ring carbon atoms inclusive and encompasses such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. The term "methylcycloalkyl" refers to the aforementioned cycloalkyl radicals containing from 3 to 8 ring carbons inclusive having a methyl substituent and encompasses such groups as 1-methylcyclopropyl, 1-methylcyclopentyl, 2-methylcyclopentyl, 3-methylcyclopentyl, 1-methylcyclohexyl, 2-methylcycloheptyl and 4-methylcyclohexyl. By the term "cycloalkenyl", it is intended to refer to those having from 4 to 8 ring carbon atoms inclusive containing a single ring carbon-carbon double bond encompassing such groups as 1-cyclobutenyl, 1-cyclopentyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl and 2-cyclohexenyl.

The term "pharmaceutically acceptable" used herein to describe an acid addition salt of a compound of Formula I refers to those salts having anionic species of a variety of relatively non-toxic inorganic or organic acids. The anion does not contribute appreciably to the toxicity of the salt or to its pharmacological activity. Illustrative of such salts are those formed with acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzenesulfonic and *p*-toluenesulfonic acids. Preparation of the mono-acid addition salts may be carried out in conventional manner by treating a solution or suspension of the free base in a reaction inert organic solvent with one chemical equivalent of the acid or if the di-acid addition salt is desired, at least two chemical equivalents of the acid. Conventional concentration of crystallization techniques are employed in isolating the salts.

A preferred group of quinazolines are those compounds of Formula I wherein R is limited to amino and R_1 is cycloalkyl.

According to the present invention, compounds of Formula I are prepared by reacting a quinazoline derivative of Formula II



Formula II

wherein substituent "A" is amino, hydrazino or halogen (preferably chlorine or bromine) and substituent "B" is halogen (preferably chlorine or bromine), piperazino, alkylthio of 1 to 4 carbon atoms inclusive or

O
"
N—(R_1C—) piperazinly

wherein R_1 is as defined above with a reactant selected from ammonia, R_1 COX and

O
"
N—(R_1C—)piperazine

wherein R_1 is as defined above and "X" is halogen (preferably chlorine or bromine) in an aqueous or reaction inert organic solvent. When A is amino or hydrazino and B is halogen or alkylthio then the reactant is

N—(R_1C—) piperazine,
"
O

when A is amino or hydrazino and B is piperazino then the reactant is R_1COX, and when A is halogen then B is

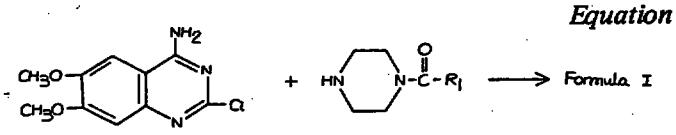
O
"
N—(R_1C—)piperazinyl and the reactant is ammonia.

Equimolar amounts of Formula II and R_1COX or N–(R_1C–)piperazine reactants are generally satisfactory, although, with ammonia, a substantial excess is preferred. The term "reaction inert solvent" as used herein refers to those organic solvents which themselves do not

enter into the reaction including such polar solvents as the aliphatic alkanols (e.g. methanol, ethanol, isopropanol, isoamyl alcohol) tetrahydrofuran, dioxane, dimethylacetamide, and dimethylformamide. When the reaction is complete, the solvent is removed by evaporation. When the resulting residue consists of a salt of Formula I, stirring with a base such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate and then purifying according to conventional crystallization techniques will provide the Formula I free base.

The following reaction schemes of Equation 1–5 illustrates the various synthetic routes embodied in the preparation of the compounds of the present invention according to the process discussed above.

Equation 1

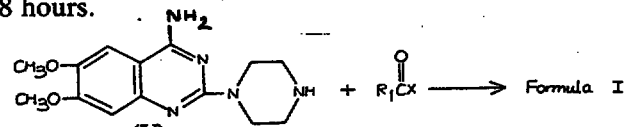


(III) (IV)

As depicted in equation 1 above, 2-chloro-4-amino-6,7-dimethoxyquinazoline of Formula III is reacted with an

O
"
N—(R_1C—)piperazine of Formula IV,

wherein R_1 is as defined above, in an inert reaction solvent in an enclosed reactor at elevated temperatures. The reaction is generally complete in a period of 16 hours at a temperature ranging from 150–180°C. but can also be carried out at temperatures of 100–180°C. for periods of 1 to 48 hours.

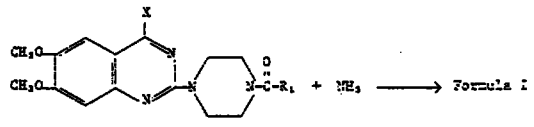


Equation 2

(V) (VI)

Equation 2 illustrates acylation of 2-piperazinyl-4-amino-6,7-dimethoxyquinazoline of Formula V with a carbonyl halide reactant of Formula VI wherein R_1 is as defined above and "X" is halogen (preferably bromine or chloride). The reaction proceeds readily at room temperature in a reaction inert organic solvent and is essentially complete after the addition of the halogenide reactant. Representative inert organic solvents which may be employed include diethyl ether, benzene, toluene, acetonitrile, halogenated hydrocarbons such as chloroform, alkanols such as methanol or ethanol, dimethylformamide and dimethyl-sulfoxide. At least a molar equivalent of the carbonyl halide reactant (VI) is employed and the reaction is stirred for a period of 1 to 6 hours following addition. The products of Formula I are filtered from the reaction mixture or isolated by conventional techniques such as evaporation of the solvent and recrystallization of the residue from alkanol solvents such as methanol, ethanol, isopropanol or chloroform.

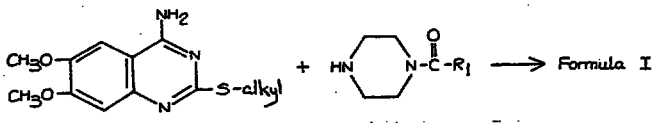
Equation 3



(VII)

Equation 3 illustrates reaction of quinazolines of Formula VII wherein R_1 is as defined above and substituent "X" is halogen, preferably chlorine or bromine, with ammonia. The reaction is carried out at 25–150°C. for a period of 16 to 36 hours in a reaction inert solvent such as tetrahydrofuran or alcohol.

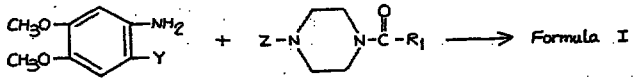
Equation 4



(VIII) (IV)

Equation 4 illustrates the reaction of a 2-alkyl-mercaptoquinazoline of Formula VIII with an N–(R_1CO)piperazine of Formula IV. The alkyl group has 1 to 4 carbon atoms, such as methyl. Preferably, the reaction is carried out in reaction inert solvent such as isoamyl alcohol at reflux temperature for a period of 16 hours.

(IX) (X)



Equation 5

The compounds of Formula I can also be obtained according to the method disclosed in German Offenlegungsschrift No. 2,457,911 which is illustraed by Equation 5. In this method, a 2-aminobenzonitrile or benzamidine of Formula IX is reacted with piperazine-1-carboxamido ester or nitrile of Formula X in a reaction inert solvent. The reaction is carried out at a temperuture of 50 to 180°C in the presence of sodium hydride. In Formula IX, "Y" represents the radical –CN or $-C(=NH)NH_2$ and in Formula X, "Z" represents the radical –CN, $-C(=NH)-OR_3$ or $-C(=NH)SR_3$ wherein R_3 is an alkyl radical of 1 to 4 carbon atoms inclusive.

The present invention also includes pharmaceutical compositions comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier. The pharmaceutical composition may be in dosage unit form adapted for the systematic administration to a mammal and comprising a dose of from 0.001 to 50 mg per kilogram of mammal body weight of said compound or salt thereof.

The 2-piperazinyl-6,7-dimethoxyquinazolines characterized by Formula I are effective antihypertensive agents having substantially less *alpha*-adrenergic blocking activity than prazosin. The invention therefore also includes a process for treating hypertension comprising systematically administering to a non-human mammal in need of treatment of an antiphertensive effective amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof. They also are phosphodiesterase inhibitors exhibiting cyclic-GMP enzyme selectivity. These desirable effects can be readily demonstrated in standard *in vitro* and *in vivo* pharmacological tests. For instance, in the spontaneous hypertensive rat, oral administration of 0.4 mg./kg. body weight of 4-amino-2-[4-(cyclopentylcarbonyl)piperazinyl]- 6,7-dimethoxyquinazoline provides at 50 mm Hg reducation in blood pressure. To obtain a similar reduction in blood pressure with prazosin, a dose of 1.8 mg./kg. body weight is required. This following table provides a pharmacological profile of 4-amino-2-[4-(cyclopentylcarbonyl)piperazinyl]-6,7-dimethoxyquinazoline wherein activity is expressed as a multiple of the activity of the reference standard prazosin taken as unity.

TABLE I

Activity of 4-Amino-2[4-(cyclopentylcarbonyl)-1-piperazinyl]-6, 7-dimethoxyquinazoline Relative to Prazosin (=1)

	Formula I (R = NH_2, R_1 = cyclopentyl) Times Prazosin
Antihypertensive potency in spontaneous hypertensive rats	4.25
Alpha-adrenergic blocking potency: in vivo (intravenous administration) in the rat versus phenylephrine	0.47
Antihypertensive/alpha blocking ratio based on: in vivo alpha block	9.0
Inhibition of cyclic nucleotide phosphodiesterase in rat heart based on in vitro determination of inhibitor constants using cyclic adenosine monophosphate or cyclic guanosine monophosphate:	
potency	2.0 – 2.5
selectivity for the cyclic GMP enzyme	2.0 – 3.5

As seen in the above table, 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline has an antihypertensive/alpha *in vivo* blocking ratio of 9.0 compared to prazosin. With respect to antihypertensive utility this is considered a very favorable ratio since it is indicative of a reduction in blood pressure without significant involvement of the *alpha* adrenergic system.

One of the most undesirable side effects encountered in antihypertensive therapy is postural hypotension which results from hemodynamic alterations induced by change from supine to erect position. Postural hypotension is generally manifested in the clinic by dizziness and/or faintness.

A useful animal model predictive of postural hypotension in man is the "dog tilt test"; refer to J. W. Constantine, et al., Am. J. Physiol. 221, No. 6, 1681–1685 (1971). In this test, anesthetized dogs monitored for blood pressure are secured to a specially constructed table on which they are rapidly tilted to a position 80–90° from the horizontal in the head-up position for 1-2 minutes. Each animal is positioned with respect to the fulcrum of the table so that the heart is approximately in the same horizontal plane in both supine and tilted positions. Prior to drug (control), tilting the animal causes an initial fall in blood pressure which is followed by a compensatory rise to or slightly above the pre-tilt level. Ten minutes after the control tilt, the drug is administered intravenously over a 3-minute period and tilt repeated. Impairment of reflex compensation to the upright position is considered to be drug induced and indicative of possible postural hypotension in humans.

Data provided by the foregoing "dog tilt test" establishes that, compared to prazosin, 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline has only 0.36 of the potential for postural hypotension at equi-antihypertensive doses.

The process of the present invention for treating hypertension is carried out by systematically administering to a mammal in need of such treatment such as those having hypertension or predisposed thereto an antihypertensive effective amount of a 2-piperazinyl-6,7-dimethoxyquinazoline characterized by Formula I or a pharmaceutically acceptable acid addition salt thereof. By systematic administration, it is intended to include both oral and parenteral routes. Examples of parenteral administration are intramuscular, intravenous, intraperitoneal, rectal, and subcutaneous administration. The dosage will vary with the form of administration and the particular compound chosen, however, from 0.001 to 50 milligrams per kilogram of body weight of the mammal of a 2-piperazinyl-6,7-dimethoxyquinazoline characterized by Formula I administered in effective single or multiple dosage units is generally satisfactory. In accordance with conventional clinical practice, an antihypertensive agent of Formula I is administered at a dosage substantially less than the dose of the compound which is thought to be effective. Thereafter, the dosage is increased by small increments until the optimum antihypertensive effect under the circumstances is reached. At effective antihypertensive dosage levels, the compounds of this invention are substantially free of postural hypotension and those harmful or deleterious side effects generally associated with *alpha*-adrenergic blockage.

In carrying out the antihypertensive process, the active ingredient of Formula I and pharmaceutically acceptable acid addition salts thereof may be administered orally in such forms as tablets, dispersible powders, granules, capsules, syrups and elixirs and parenterally as solutions, suspensions, dispersions and emulsions. The compositions for oral use may contain one or more conventional adjuvants, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a composition of suitable pharmaceutical elegance. Tablets may contain the active ingredient in admixture with conventional pharmaceutical acceptable excipients including inert diluents such as calcium carbonate, sodium carbonate, lactose and talc; granulating and disintegrating agents such as starch alginic acid; binding agents such as starch, gelatin and acacia and lubricating agents such as magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Similarly, suspensions, syrups, and elixirs may contain the active ingredient in admixture with any of the conventional excipients utilized for the preparation of such compositions such as suspending agents (e.g., methylcellulose, tragacanth, and sodium alginate), wetting agents (e.g., lecithin, polyoxyethylene stearate) and preservations such as ethyl-*p*-hydroxybenzoate. Capsules may contain the active ingredient alone or admixed with an inert solid diluent such as calcium carbonate, calcium phosphate and kaolin. The injectible compositions are formulated as known in the art and may contain appropriate dispersing or wetting agents and suspending agents identical or similar to those mentioned above.

The following examples are given by way of illustration.

EXAMPLE 1

4-Amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline

(a) A mixture of N-(cyclopentylcarbonyl)piperazine (3.6 g., 0.02 mole) and 2-chloro-4-

amino-6,7-dimethoxyquinazoline (4.79 g., 0.02 mole) in 50 ml. of absolute ethanol is heated in an enclosed reactor at 170°C. for a period of 16 hours to provide the hydrochloride salt. The reaction mixture is cooled, filtered and insolubles triturated with 100 ml. of concentrated ammonium hydroxide to provide the free base. The insoluble product is collected and crystallized from methanol to afford analytically pure 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline, m.p. 256. 0-259.0, C (corr.).

Analysis. Calcd. for $C_{20}H_{27}N_5O_3$ (percent): C, 62.32; H, 7.06; N, 18.17. Found (percent): C, 62.06; H, 7.24; N, 17.99.

Example 1(a) illustrates the procedure of aforementioned Equation 1 while the following Examples 1 (b–e) illustrate procedures of Equations 2–5, respectively, for the preparation of 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline.

(b) Cyclopentylcarbonyl chloride (0.1 mole) is added to 0.1 mole of 4-amino-2-(1-piperazinyl)-6,7-dimethoxyquinazoline in 300 ml. of methanol with vigorous stirring at room temperature. Stirring is continued for a period of 2 to 6 hours and the product is isolated according to the procedure of Example 1(a) to provide 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline. If the hydrochloride salt is desired, the base treatment is omitted and evaporation of the solvent provides 4-amino-2-[4-(cyclopentycarbonyl)-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride, m.p. 279–280°C. (dec.)(corr.) crystallized from methanol-isopropanol.

Analysis. Calcd. for $C_{20}H_{27}N_5O_3$ HCl (percent): C, 56.93; H, 6.69; N, 16.60. Found (percent): C, 56.65: H, 6.89; N, 16.44.

(c) A mixture of anhydrous ammonia and 4-chloro-2-[4-(cyclopenylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline in 100 ml. of tetrahydrofuran is heated at 100°C for a period of 16 to 24 hours and the product is isolated to according to the procedure of Example 1(a) to provide 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline.

(d) A mixture of 4-amino-2-methylmercapto-6,7-dimethoxyquinazoline (0.1 mole) and from 0.1 to 0.15 nole of N–(cyclopentylcarbonyl)piperazine in 150 ml. of isoamyl alcohol is refluxed for a period of 8 to 24 hours. The solvent is evaporated and residual material, tested according to procedure of Example 1(a), provides 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxy-quinazoline.

(e) Ethyl-4-(cyclopentylcarbonyl)piperazin-1-yl-formamidate hydrochloride (0.01 mole) is added to a solution of 4,5-dimethoxy-2-aminobenzonitrile (0.01 mole) in 30 ml. of N,N-dimethylformamide. Sodium hydride (0.02 mole of a 56% suspension in mineral oil) is added and the mixture stirred 0.5 hr. at room temperature and then at 100°C for a period of 12 hr. When the reaction period is complete, wter is added providing 4-amino-2-[4-cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline.

EXAMPLE 2

4-Amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline

N-(Cyclopentylcarbonyl)piperazine (3.08 g., 0.02 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (4.79 g., 0.02 mole) are reacted according to the procedure of Example 1(a). The crude product crystallized from ethanol affords analytically pure 4-amino-2-[4-(cyclopropylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline, m.p. 283.5–2.85.5°C. (corr.).

Analysis. Calcd. for $C_{18}H_{23}N_5O_3$ (percent): C, 60.49; H, 6.49; N, 19.59. Found (percent): C, 60.56; H, 6.46; N, 19.41.

EXAMPLE 3

4-Amino-2-[4-(cyclohexylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline

N-(Cyclohexylcarbonyl)piperazine (5.9 g., 0.03 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (7.2 g., 0.03 mole) are reacted according to the procedure of Example 1(a). The crude product crystallized from methanol affords analytically pure 4-amino-2-[4-(cyclohexylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline, m.p. 223–225°C., resolidifying and remelting at 248.0-250.0°C. (corr.);

Analysis. Calcd. for $C_{21}H_{29}N_5O_3$ (percent): C, 63.14; H, 7.32; N, 17.53. Found (percent): C, 63.07; H, 7.43; H, 17.63.

EXAMPLE 4

4-Amino-2-[4-(1-cyclopenten-1-ylcarbonyl)-piperazinyl]-6,7-dimethoxyquinazoline

N-(1-cyclopenten-1-ylcarbonyl)piperazine (1.8 g., 0.01 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (2.4 g., 0.01 mole) are reacted according to the procedure of Example 1(a). The isolated product crystallized from methanol affords analytically pure 4-amino-2-[4-(1,cyclopenten-1-ylcarbonyl)piperazinyl]-6,7-dimethoxy-quinazoline, m.p. 256.5–258.0°C. (Corr.).

Analysis. Calcd. for $C_{20}H_{25}N_5O_3$ (percent): C, 62.65; H, 6.57; N, 18.26. Found (percent): C, 62.53; H, 6.56; N, 18.42.

EXAMPLE 5

4-Amino-2-[4-(3-cyclopentenylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline

N-(3-cyclopentenylcarbonyl)piperazine (2.7 g., 0.015 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (3.6. g., 0.015 mole) are reacted according to the procedure of Example 1(a). The crude product crystallized from methanol affords analytically pure 4-amino-2-[4-(3-cyclopentenylcarbonyl)-1-qiperazinyl]-6,7-dimethoxyquinazoline, m.p. 215.5–217.5°C. (corr.).

Analysis: Calcd. for $C_{20}H_{25}N_5O_3$ (percent): C, 62.65; H, 6.57; N, 18.26. Found (percent): C, 62.35; H, 6.72; N, 18.21.

EXAMPLE 6

4-Amino-2-[4-(3-cyclohexenylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline

N-(3-cyclohexenylcarbonyl)piperazine (7.65 g., 0.04 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (9.6 g., 0.04 mole) are reacted according to the procedure of Example 1(a). The crude product crystallized from methanol afforfs analytically pure 4-amino-2-[4-(3-cyclohexenylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline, m.p. 211-213°C. resolidifying and melting at 234.0–236.0°C. (corr.).

Analysis. Calcd. for $C_{21}H_{27}N_5O_3$ (percent): C, 63.46; H. 6.85; N, 17.62. Found (percent): C, 63.18; H, 6;80; N, 17.63.

EXAMPLE 7

4-Amino-2-[4-(cyclobutylcarbonyl)-1-piperazinyl]-6,7-dimethyxyquinazoline Hydrochloride

N-(cyclobutylcarbonyl)piperazine (0.02 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (0.02 mole) are reacted according to the procedure of Example 1(a) to provide the hydrochloride salt but without conversion to the free base. When reaction is complete, the solvent is removed and the residue crystallized from methanol-isopropanol to provide analytically pure 4-amino-2-[4-(cyclobutyl-carbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride hydrate, m.p. 267–268°C. (dec.) (corr.).

Analysis. Calcd. for $C_{19}H_{25}N_5O_3 \cdot HCl \cdot 1/4H_2O$ (percent): C, 55.33; H, 6.48; N, 16.98. Found (percent): C, 55.49; H, 6.75; N, 16.62.

EXAMPLE 8

4-Amino-2-[4-(cycloheptylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Hydrochloride

N-(Cycloheptylcarbonyl)piperazine (0.02 mole) and 2-chloro-4-amino-6,7-dimethoxyquinazoline (0.02 mole) are reacted according to the procedure of Example 7. Crystallization of the product from methanol-isopropanol provides analytically pure 4-amino-2-[4-(cycloheptycarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride, m.p. 278–279°C. (corr.).

Analysis. Calcd. for $C_{22}H_{31}N_5O_3 \cdot HCl$ (percent): C, 58.72; H, 7.17; N, 15.56. Found (percent): C, 58.73; H, 7.39; N, 15.44.

EXAMPLE 9

Following the procedure of Example 1 but employing an equimolar amount of:
N-(2-cyclopentylcarbonyl)piperazine
N-(1-cyclohexen-1-ylcarbonyl)piperazine,
N-(cyclooctylcarbonyl)piperazine,
N-(2-methylcyclopentylcarbonyl)piperazine,
N-(1-methylcyclopentylcarbonyl)piperazine,
N-(1-methylcyclohexylcarbonyl)piperazine,
in place of N-(cyclopentylcarbonyl)piperazine, there is produced:
(a) 4-amino-2-[4-(2-cyclopentenylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline,
(b) 4-amino-2-[4-(1-cyclohexen-1-ylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline,
(c) 4-amino-2-[4-(cyclooctylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline,
(d) 4-amino-2-[4-(2-methylcyclopentylcarbonyl)-1-piperazinyl]6,7-dimethoxyquinazoline,
(e) 4-amino-2-[4-(1-methylcyclpentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline,
(f) 4-amino-2-[4-(1-methylcyclohexylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline.

EXAMPLE 10

4-Hydrazino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Hydrochloride

N-(Cyclopentylcarbonyl)piperazine (0.02 mole) and 2-chloro-4-hydrazino-6,7-dimethoxyquinazoline (0.02 mole) reacted according to the procedure of Example 7 provides 4-hydrazino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride, m.p. 282–284°C.

EXAMPLE 11

Suspensions

A suspension of 4-amino-2-[4-(cyclppentylcarbonyl)-1-piperazinyl]-6,7-

dimethoxyquinazoline or a pharmaceutically acceptable salt thereof is prepared with the following ingredients:

Active ingredient	20 g.
Sucrose, U.S.P.	400 g.
Sorbitol, U.S.P.	100 g.
Bentonite	20 g
Flavors, q.s.	
Water, distilled to make one liter	

Each milliliter of the suspension contains approximately 20 mg. of the active ingredient.

EXAMPLE 12

Tablets

The following ingredients are blended in the proportion by weight indicated according to conventional pharmaceutical techniques to provide a tablet base.

Lactose	79
Corn starch	10
Talcum	6
Tragancanth	4
Magnesium Stearate	1

This tablet base is blended with sufficient 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable salt thereof to provide tablets containing 0.1, 0.25, 0.5, 1, 2.5, 5, 7.5, 10, 25, and 50 mg. of active ingredient; formed in a tablet of the desired size in a conventional tablet press.

EXAMPLE 13

Dry Filled Capsules

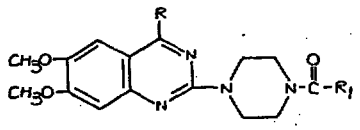
The following ingredients are blended in a conventional manner in the proportion by weight indicated.

Lactose	50
Starch	5
Magnesium stearate	2

Sufficient 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable salt thereof is added to the blend to provide capsules containing 0.1, 0.25, 0.5, 1, 2.5, 5, 7.5, 10, 25, and 50 mg. of active ingredient, and filled into hard gelatin capsules of a suitable size.

WHAT WE CLAIM IS:–

1. A compound having the formula



I

or a pharmaceutically acceptable acid addition salt thereof wherein

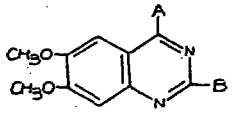
R is amino or hydrazino;

R_1 is cycloalkyl or methylcycloalkyl having 3 to 8 ring carbon atoms inclusive or cycloalkenyl having 4 to 8 ring carbon atoms inclusive.

2. 4-Amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.

3. 4-Amino-2-[4-(cyclopentylcarbonyl-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride.

4. A process for the preparation of a compound according to Claim 1 characterized by reacting a quinazoline derivative of formula



II

wherein

A is amino, hydrazino or halogen;

B is halogen, piperazino, alkylthio of 1 to 4 carbon atoms inclusive or

dimethoxyquinazoline or a pharmaceutically acceptable salt thereof is prepared with the following ingredients:

Active ingredient	20 g.
Sucrose, U.S.P.	400 g.
Sorbitol, U.S.P.	100 g.
Bentonite	20 g
Flavors, q.s.	
Water, distilled to make one liter	

Each milliliter of the suspension contains approximately 20 mg. of the active ingredient.

EXAMPLE 12

Tablets

The following ingredients are blended in the proportion by weight indicated according to conventional pharmaceutical techniques to provide a tablet base.

Lactose	79
Corn starch	10
Talcum	6
Tragancanth	4
Magnesium Stearate	1

This tablet base is blended with sufficient 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable salt thereof to provide tablets containing 0.1, 0.25, 0.5, 1, 2.5, 5, 7.5, 10, 25, and 50 mg. of active ingredient; formed in a tablet of the desired size in a conventional tablet press.

EXAMPLE 13

Dry Filled Capsules

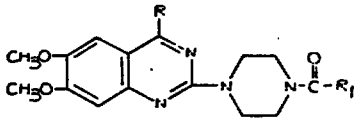
The following ingredients are blended in a conventional manner in the proportion by weight indicated.

Lactose	50
Starch	5
Magnesium stearate	2

Sufficient 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable salt thereof is added to the blend to provide capsules containing 0.1, 0.25, 0.5, 1, 2.5, 5, 7.5, 10, 25, and 50 mg. of active ingredient, and filled into hard gelatin capsules of a suitable size.

WHAT WE CLAIM IS:–

1. A compound having the formula



I

or a pharmaceutically acceptable acid addition salt thereof wherein

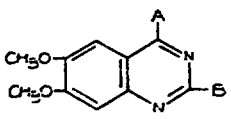
R is amino or hydrazino;

R_1 is cycloalkyl or methylcycloalkyl having 3 to 8 ring carbon atoms inclusive or cycloalkenyl having 4 to 8 ring carbon atoms inclusive.

2. 4-Amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.

3. 4-Amino-2-[4-(cyclopentylcarbonyl-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride.

4. A process for the preparation of a compound according to Claim 1 characterized by reacting a quinazoline derivative of formula



II

wherein

A is amino, hydrazino or halogen;

B is halogen, piperazino, alkylthio of 1 to 4 carbon atoms inclusive or

N—(R_1C—)piperazinyl wherein R_1 is as defined in Claim 1 with a reactant selected from ammonia, R_1COX and

N—(R_1C—)piperazine

wherein R_1 is defined as above and X is halogen, in an aqueous or reaction inert organic solvent, with the provisos that (a) when A is amino or hydrazino and B is halogen or alkylthio then the reactant is

N—(R_1C—)piperazine,

(b) when A is amino or hydrazino and B is piperazino then the reactant is R_1COX, and (c) when A is halogen then B is

N—(R_1C—)piperazinyl and the reactant is ammonia,

and where the reactcon product is a salt of the compound of formula I and the free base is desired, optionally basifying said salt by methods known per se to produce the free base of the compound of formula I.

5. A process according to Claim 4 wherein
A is H_2N– and
B is Cl–
in said compound of formula II and said reactant is

N—(R_1C—)piperazine

6. A process according to Claim 4 wherein
A is H_2N– and
B is piperazino
in said compound of formula II and said reactant is R_1COX.

7. A process according to Claim 4 wherein
A is halogen and
B is N—(R_1C—)piperazine
in said compound of formula II and said reactant is ammonia.

8. A process according to Claim 4 wherein
A is H_2N– and
B is alkylthio of 1 to 4 carbon atoms inclusive in said compound of formula II and said reactant is

N—(R_1C—)piperazine.

9. A process according to Claim 4 wherein the product of formula I is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.

10. A process according to Claim 4 wherein the product of formula I is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride.

11. A process for treating hypertension which comprises systematically adiministering to a non-human mammal in need of said treatment an antihypertensive effective amount of a compound according to Claim 1.

12. The process of Claim 11 wherein said compound is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.

13. The process of Claim 11 wherein said compound is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride.

14. A pharmaceutical composition in dosage unit form adapted for the systemic administration to a mammal comprising a dose of from 0.001 to 50 mg. per kilogram of body weight of said mammal of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

15. The composition of Claim 14 wherein said compound is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline or a pharmaceutically

acceptable acid addition salt thereof.

16. The composition of Claim 14 wherein said compound is 4-amino-2-[4-(cyclopentylcarbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline hydrochloride.

17. A compound having the formula I or a pharmaceutically acceptable acid addition salt thereof substantially as described herein with reference to any one of examples 1 to 10.

18. A process for the preparation of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof substantially as described herein with reference to any one of Examples 1 to 10.

19. A process according to Claim 4 substantially as described herein.

20. A compound of formula I or a pharmaceutically acceptable acid addition salt thereof when prepared by the process of any one of Claims 4 to 10, 18 or 19.

21. A process for treating hypertension which comprises systematically administering to a non-human mammal in need of treatment an antihypertensive effective amount of a compound according to any one of Claims 1 to 3, 17 or 20, or a pharmaceutically acceptable acid addition salt thereof.

22. A pharmaceutical composition comprising an effective amount of a compound according to any one of Claims 1 to 3, 17 or 20 or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier.

23. A pharmaceutical composition according to Claim 22 in the form of a suspension, tablets or dry filled capsules.

24. A suspension, tablets or dry filled capsules substantially as described herein with reference to Example 11, 12 or 13.

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