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PATENT SPECIFICATION

NO DRAWINGS

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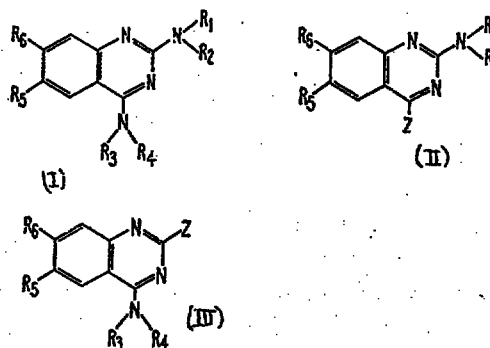
COMPLETE SPECIFICATION

Quinazoline Derivatives

We, CHAS. PFIZER & CO., INC. a Corporation organized under the laws of the State of Delaware, United States of America, of 235, East 42nd Street, New York 17, New York, 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 relates to new and useful compounds which are valuable therapeutic agents. More particularly, it is the object of this invention to provide new and useful chemotherapeutic agents valuable in reducing blood pressure in hypertensive subjects.

In accordance with the present invention, compounds found to have valuable hypotensive properties are those of the following formulae:

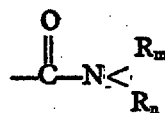


wherein R_1 , R_2 , R_3 and R_4 are hydrogen, alkyl having from 1 to 5 carbon atoms, alkenyl having from 3 to 5 carbon atoms, propargyl, phenyl, hydroxyalkyl having from 1 to 5 carbon atoms, alkoxyphenyl having from 7 to 12 carbon atoms, benzyl, phenylethyl, alkyl or dialkyl substituted-phenyl where alkyl has from 1 to 6 carbon atoms, chlorophenyl, bromophenyl, fluorophenyl, hydroxyphenyl, dichlorophenyl, dibromophenyl, difluorophenyl or 2,2,2-trifluoroethyl;

R_5 and R_6 are hydrogen, alkoxy having from 1 to 5 carbon atoms, alkyl having from 1 to 3 carbon atoms, at least one of R_5 and R_6 being alkyl or alkoxy, or wherein R_5 and R_6 together are benzo or an alkylendioxy group, (with the proviso that in a quinazoline of Formula I herein when R_5 and R_6 are both methoxy and R_3 and R_4 are both hydrogen, then R_1 and R_2 may not both be methyl or hydrogen), the preferred compounds are those where at least one of R_5 and R_6 are alkoxy having from 1 to 3 carbon atoms; or wherein R_5 and R_6 together are benzo;

Z is 1-piperazinyl, 4-alkyl-1-piperazinyl where alkyl has from 1 to 5 carbon atoms, 4-hydroxyalkyl-1-piperazinyl where alkyl has from 1 to 5 carbon atoms, 4-alkanoyl-1-piperazinyl where alkanoyl has from 2 to 7 carbon atoms, 3-oxo-1-piperazinyl, 4-benzoyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 4-allyl-1-piperazinyl, morpholino, 2,6-dialkylmorpholino where alkyl has from 1 to 5 carbon atoms, 1-pyrrolidinyl, 1-azacycloheptyl, 1-azacyclooctyl, piperidino, 2-hydroxy-piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 2-alkoxypiperidino, 3-alkoxypiperidino, and 4-alkoxypiperidino where alkoxy has from 1 to 4 carbon atoms, 2-alkylpiperidino, 3-alkylpiperidino, and 4-alkylpiperidino where alkyl has from 1 to 6 carbon atoms, 2-benzylpiperidino, 4-benzylpiperidino, 2-hydroxyalkylpiperidino, 3-hydroxyalkylpiperidino, and 4-hydroxyalkylpiperidino where alkyl has from 1 to 6 carbon atoms, 4-(2-halophenyl)-1-piperazinyl, 4-(3-halophenyl)-1-piperazinyl, 4-(4-halophenyl)-1-piperazinyl, 4-(2-halobenzoyl)-1-piperazinyl, 4-(3-halobenzoyl)-1-piperazinyl or 4-(4-halobenzoyl)-1-piperazinyl where halo is chloro or bromo, 4-piperazinyl-1-carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms, 4-piperazinyl-1-carboxylic acid alkenyl ester where alkenyl has from 2 to 6 carbon atoms, 4-(2-furoyl)-1-piperazinyl, 4-(3-furoyl)-1-piperazinyl, 4-(2-thenoyl)-1-piperazinyl, 4-(3-thenoyl)-1-piperazinyl, 4-(2-methylallyl)-1-piperazinyl, 4-crotonyl-1-piperazinyl, cycloalkylamino where alkyl has from 3 to 7 carbon atoms, 4-carbamoyl-1-piperazinyl where carbamoyl has the formula:

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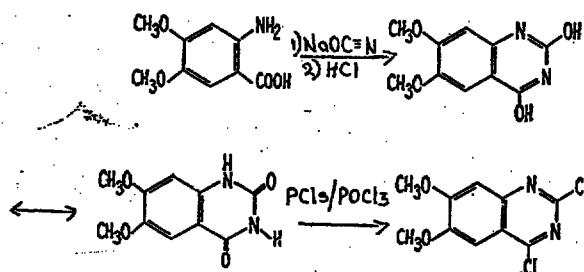


where R_m and R_n are hydrogen or alkyl having from 1 to 6 carbon atoms, 4-(2-methoxyphenyl)-1-piperazinyl, 4-(3-methoxyphenyl)-1-piperazinyl, 4-(4-methoxyphenyl)-1-piperazinyl, 4-(2-trifluoromethylphenyl)-1-piperazinyl, 4-(3-trifluoromethylphenyl)-1-piperazinyl, 4-(4-trifluoromethylphenyl)-1-piperazinyl, 4-(2-methylphenyl)-1-piperazinyl, 4-(3-methylphenyl)-1-piperazinyl, 4-(4-methylphenyl)-1-piperazinyl, 4-(2-methylbenzoyl)-1-piperazinyl, 4-(3-methylbenzoyl)-1-piperazinyl, 4-(4-methylbenzoyl)-1-piperazinyl, 4-(2-trifluoromethylbenzoyl)-1-piperazinyl, 4-(3-trifluoromethylbenzoyl)-1-piperazinyl, 4-(4-trifluoromethylbenzoyl)-1-piperazinyl, 4-(2-methoxybenzoyl)-1-piperazinyl, 4-(3-methoxybenzoyl)-1-piperazinyl, 4-(4-methoxybenzoyl)-1-piperazinyl, and the pharmaceutically-acceptable acid addition salts thereof.

Of the preceding compounds, 2-dimethylamino-4-amino-6,7-dimethoxyquinazoline dihydrochloride has been tested and reported by J. D. Thayer, et al in *Antibiotics and Chemotherapy*, Vol. II, No. 9, Sept. 1952, p. 463-466 as an antibacterial agent and found to have a slight order of activity. However, it is the existence of this compound in the aforesaid prior art which necessitates our excluding this compound from the compound claims of this invention.

The compounds of this invention are particularly effective in reducing blood pressure in hypertensive subjects. On tests with renal hypertensive dogs, as little as 0.06 mg. of active ingredient per kilogram of body weight was found effective in reducing blood pressure from 180/100 to 160/100 mm. Hg. The results of these tests are shown in the examples below. These compounds are prepared by the cyclization of ureido derivatives of various aromatic acids, amides, nitrile and esters with an aqueous base or acid. The ureido derivatives are obtained by reacting the aromatic compound with sodium or potassium cyanate or by reacting the aromatic acid with urea according to the procedure of F. H. S. Curd, et al in the *Journal of the Chemical Society (London)*, 1947 p. 777.

After cyclization, the resulting 2,4-dihydroxyquinazoline is chlorinated at the 2- and 4-positions with a mixture of phosphorus pentachloride and phosphoryl chloride or with a mixture of phosphoryl chloride in N,N-dimethylaniline. The preparation of 2,4-dichloro-6,7-dimethoxyquinazoline from 4,5-dimethoxyanthranilic acid is shown in the following sequence:



The substituents are controlled to a great extent by the substituents on the starting aromatic acid, amide, nitrile or ester. Typical 2,4-dichloroquinazolines, obtained by cyclization and chlorination, and their starting compounds are given in Table I.

TABLE I

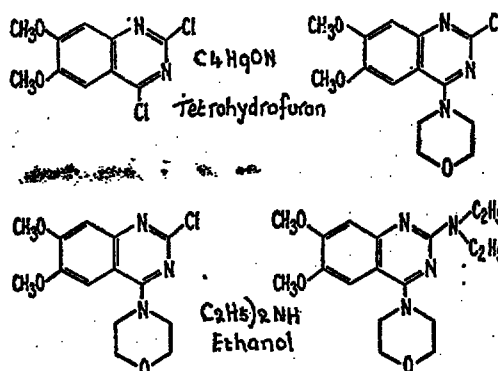
Substituted 2,4-Dichloroquinazolines

Starting Compounds	Substituent
5-methoxyanthranilic acid	6-methoxy-
4-methoxyanthranilamide	7-methoxy-
methyl 4-methoxyanthranilate	7-methoxy-
4-methoxyanthranilic acid	7-methoxy-
4-amyloxyanthranilic acid	7-amyloxy-
5-amyloxyanthranilic acid	6-amyloxy-
6-aminoveratric acid	6,7-dimethoxy-
4,5-diamyloxyanthranilic acid	6,7-diamyloxy-
5-methylantranilic acid	6-methyl-
4-methylantranilic acid	7-methyl-
4-ethylantranilic acid	7-ethyl-
4-n-propylantranilic acid	7-n-propyl-
4-isopropylantranilic acid	7-isopropyl-
5-n-propylantranilic acid	6-n-propyl-
4,5-dimethylantranilic acid	6,7-dimethyl-
4,5-di-n-propylantranilic acid	6,7-di-n-propyl-

The process employed for preparing the novel compounds of this invention involves treating the corresponding 2,4-dichloroquinazoline with the appropriate amine base. The 2-chloro-4-aminoquinazolines are prepared by reacting equimolar quantities of ammonia in tetrahydrofuran and 2,4-dichloroquinazoline. However, in ordinary practice a preferred excess of ammonia would be from one to ten moles in order to shift the reaction to completion. Appropriate amines and nitrogenous heterocyclic compounds are likewise reacted with the dichloro compound to yield 2-chloro-4-substituted-quinazolines. The temperature at which this reaction can be conducted varies from 25 to about 200°C. for a period of from one hour to 48 hours. A preferred reaction temperature and time for this reaction would be about 25—60°C. for about four hours. Upon completion of reaction the product is recovered by conventional means. For instance, the solvent can be evaporated and the crude solid can be triturated with water or precipitated from dilute aqueous acid in crystalline form and subsequently recrystallized from any number of appropriate organic solvents such as methanol or dimethylformamide.

Replacement of chlorine in the 2-position of the quinazoline nucleus is accomplished by reaction of the 2-chloro-4-aminoquinazoline or 2-chloro-4-substituted quinazoline with ammonia or an appropriate amino compound such as piperidine in an aqueous or an organic solvent. A molar excess of base is generally employed, while preferred organic solvents for these purposes include polar solvents, such as tetrahydrofuran, dioxane, dimethylacetamide, dimethylformamide, or alcohols such as methanol and ethanol. The reaction mixture is heated from 100 to 160°C. for from 1 to 65 hours in a sealed pressure bottle. A preferred time and temperature is 140°C. and 4 hours for an alkylamine or heterocyclic compound and 160°C. for 65 hours for ammonia in ethanol. After the reaction is complete, the solvent is evaporated and

the product is recrystallized from a mixture of an organic solvent and water. For instance, methanol/water. The reaction is illustrated by the following steps.



The well known procedures for preparing salts of basic compounds are also applicable for the compounds of this invention and are illustrated in the examples below. Such salts may be formed with both pharmaceutically-acceptable and pharmaceutically-unacceptable acids. By "pharmaceutically-acceptable" is meant those salt-forming acids which do not substantially increase the toxicity of the basic compound. The preferred salts are the acid addition salts. These salts are of particular value in therapy. They include salts of mineral acids such as hydrochloric, hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, gulonic, succinic and arylsulfonic, e.g. para-toluenesulphonic, acids.

The pharmaceutically-unacceptable acid addition salts, while not useful for therapy, are valuable for isolation and purification of the newly recognized biologically-active compounds. Furthermore, they are useful for the preparation of the pharmaceutically-acceptable salts. Of this group, the more common salts include those formed with hydrofluoric and perchloric acids. Hydrofluoride salts are particularly useful for the preparation of the pharmaceutically-acceptable salts, e.g. the hydrochloride, by solution in hydrochloric acid and crystallization of the hydrochloride salt formed. The perchloric acid salts are useful for purification and crystallization of the new compounds.

While the procedures described above are preferred for preparing the compounds of this invention on the basis of improved yields, alternate methods may also be used. The alternative methods may be divided into eight groups for convenience:

1. Halogenation of a 6- R_s -7- R_e -2-Z (or $-NR_2$)-3,4-dihydroquinazoline-4-one to yield the corresponding substituted -4-haloquinazoline, followed by reaction with an appropriate nitrogen-containing compound at position 4.

2. Thiolation of a 6- R_s -7- R_e -(1H,3H)-quinazoline-2,4-dione with or without subsequent alkylation or benzylation and reaction with an appropriate nitrogen-containing compound.

3. Alkylation, alkanoylation, aroylation and arylation of a piperazino group attached to position 2 or 4 of the quinazoline nucleus.

4. Reaction of an appropriate guanidine with 2-amino-4- R_e -5- R_s -benzonitriles to form 2-amino-4-substituted-6- R_s -7- R_e -quinazolines.

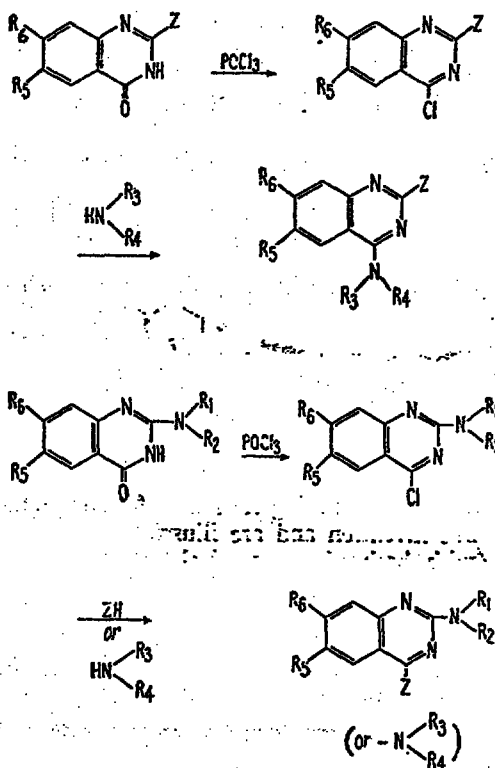
5. Reaction of appropriate guanidines with 2-chloro-4- R_e -5- R_s -benzonitriles to form 2-substituted-4-amino-6- R_s -7- R_e -quinazolines.

6. Reaction of appropriate guanidines with 2-amidino-4- R_e -5- R_s -anilines to form 2-substituted-4-amino-6- R_s -7- R_e -quinazolines.

7. Reaction of 2-chloro-4-alkoxy-6- R_s -7- R_e -quinazolines with ammonia or amino compounds to form 2,4-disubstituted-6- R_s -7- R_e -quinazolines.

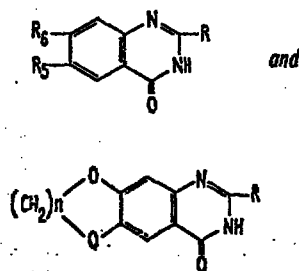
8. Reaction of 2-chloro-4-alkylthio-6- R_s -7- R_e -quinazolines with ammonia or amino compounds to form 2,4-disubstituted-6- R_s -7- R_e -quinazolines.

In method (1), 3,4-dihydroquinazoline-4-ones are halogenated with reagents such as phosphorus oxychloride, phosphorous oxybromide, phosphorous trichloride, phosphorous pentachloride or thionyl chloride, to produce the corresponding 4-haloquinazoline which is then reacted with an amine or heterocyclic compound according to the procedures previously described herein. The following sequence illustrates this method:



where R₁, R₂, R₃, R₄, R₅, R₆ and Z are as previously defined. In this method, a molar equivalent amount, and preferably an excess, of one of the aforementioned halogenating agents is added to the 3,4-dihydroquinazoline-4-one or an acid addition salt such as the hydrochloride, sulfate, phosphate or hydrobromide. The reagent is added slowly to the quinazoline at room temperature and then the mixture is refluxed for from about 30 minutes to about 2 hours. The latter time is sufficient for samples of about 10 grams of the quinazoline. Of course, longer reflux periods are desirable for larger batches in order to ensure complete reaction. The liquids are evaporated and the resulting crystalline residue is then redissolved in a dilute aqueous solution of sodium bicarbonate, sodium carbonate, sodium hydroxide or the corresponding potassium salts. The aqueous solution is extracted with a solvent such as chloroform or ethyl ether. While the specific extractant is not an essential part of the process, chloroform is preferred on the basis of convenience and safety. The combined extracts are dried with a drying agent such as sodium sulfate or potassium carbonate and the solvent is evaporated to yield the quinazoline substituted with chlorine or bromine on position 4. The resulting compound is reacted with ammonia, amines or heterocyclic compounds by any of the aforementioned methods.

The 3,4-dihydroquinazoline-4-ones are prepared by reacting the corresponding 2-halo-3,4-dihydroquinazoline-4-one with a suitable amine base. Preferred starting materials are 2-amino-3,4-dihydroquinazoline-4-one of the formula

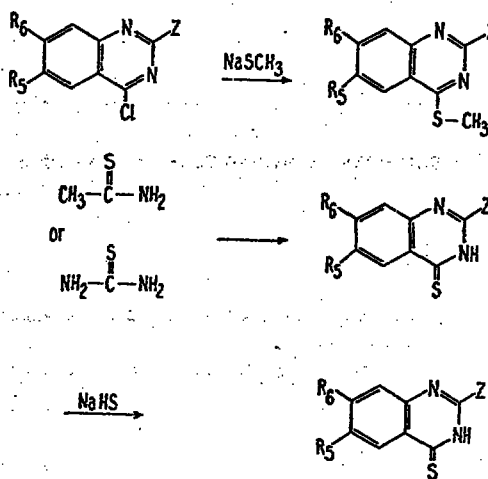


wherein R_5 and R_6 are as previously defined, and R is amino, N-monoalkylamino, N,N-dialkylamino, N-monohydroxyalkylamino, N,N-di(hydroxyalkyl)amino, N-mono-alkenylamino, N,N-dialkenylamino, N-alkenyl-N-alkylamino, N-alkyl-N-phenylamino, N-alkyl-N-(p-tolyl)amino, pyrrolidino, piperidino, homopiperidino, morpholino, 2,6-dimethylmorpholino, piperazino, N'-alkylpiperazino or N'-phenylpiperazino, each alkyl and alkenyl group in R containing up to five carbon atoms with the alkenyl containing at least 3 carbons, which are prepared by reacting the corresponding 2-halo-3,4-dihydroquinazoline-4-one with an amine base of the formula:

RH

where R is as defined above.

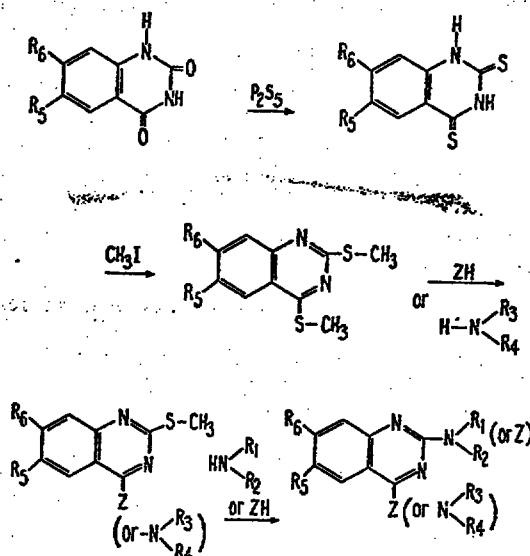
An alternate procedure involving this method, consists in reacting the 4-haloquinazoline with at least a molar equivalent amount of sodium sulfide, thiourea, thioacetamide or sodium methyl mercaptan. Sodium sulfide is reacted from an aqueous solution, sodium methyl mercaptan may be reacted either from aqueous solution or alkanol solution such as methanol, ethanol or isopropanol. Thiourea and thioacetamide are reacted from alkanol solution and ethanol is most convenient. The reaction of the 4-haloquinazoline with these sulfur-containing compounds is accomplished at reflux for from about 2 to 8 hours, depending on the size of the samples. The reactions proceed according to the following sequence:



where R_5 , R_6 and Z are as previously disclosed and where Z may also be N^{R_1} or N^{R_2}

where R_1 and R_2 are as previously disclosed. The reaction products are allowed to precipitate from the cooled reaction mixture and may be recrystallized from such solvents as ethanol-water mixtures. The recrystallized and dried products may then be reacted with heterocyclic compounds, ammonia or amines according to the procedures previously described for reacting the 4-haloquinazolines to obtain nitrogen substituents on position 4.

In method (2) a 6- R_5 -7- R_6 -(1H,3H)-quinazoline-2,4-dione is reacted with a reagent such as phosphorus pentasulfide to form the 2,4-dithioquinazoline which in turn is reacted with an alkyl or benzyl halide to form the alkylthio or benzylthio derivative. The alkylthio or benzylthio derivative is then reacted with ammonia, an amine or a heterocyclic compound by the procedures previously described for the reaction of 2,4-dichloroquinazoline to form nitrogen-containing substituents on positions 2 and 4 of the quinazoline nucleus. This method is illustrated by the following sequence:

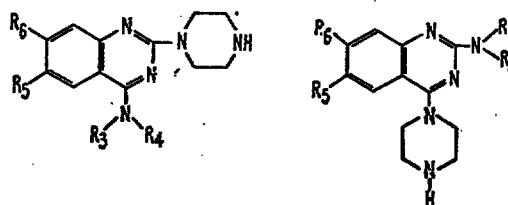


where $R_1, R_2, R_3, R_4, R_5, R_6$ and Z are as previously described.

The compounds of this invention are prepared by reacting at least a molar equivalent amount of phosphorous pentasulfide with the quinazoline-2,4-dione and preferably an excess of the pentasulfide to ensure complete reaction. While the quinazoline may be dissolved in any non-reactive solvent, the use of a pyridine solution is preferred. The pentasulfide is added to the stirred solution at room temperature and then refluxed with continual stirring. As in the previous method, the reflux time is dependent on the size of the sample. After refluxing, the solvent is removed under reduced pressure, the residue is decomposed with hot water and the solid dithione is filtered from the mixture. To the dithione is added a solvent mixture of aqueous base and an alkanol. Bases useful in this method are sodium hydroxide and potassium hydroxide. Methanol, ethanol, isopropanol and butyl alcohol are useful in this method and methanol is preferred on the basis of its low boiling point. To the solution is slowly added with stirring at least a twice-molar equivalent of an alkylating agent selected from alkyl iodides, alkyl chlorides, alkyl bromides and the corresponding benzyl halides. Methyl and benzyl iodide, are preferred. The mixture is heated to the boiling point of water for about 2 hours. For large samples and for lower temperatures, the time may be extended. The mixture is cooled and the precipitated product is filtered from the mixture. The resulting 2,4-dialkyl- or 2,4-dibenzylmercaptoquinazoline is reacted with ammonia, amines or heterocyclic compounds according to any of the previously described processes for reacting 2,4-dichloroquinazolines, to obtain the compounds of this invention.

These compounds may also be prepared by reacting the dithione directly with ammonia, amines or a heterocyclic nitrogen compound and equivalent yields of product are obtained thereby.

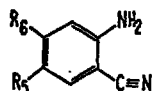
In method (3), compounds of the formulae:



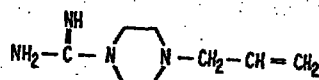
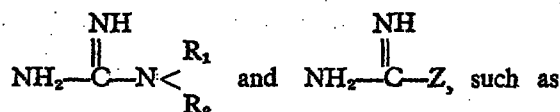
where R_1, R_2, R_3, R_4, R_5 and R_6 are as previously described are reacted, for example, with alkyl chlorides and alkyl bromides where alkyl has from 1 to 5 carbon atoms, alkanoyl bromides and alkanoyl chlorides where alkanoyl has from 2 to 7 carbon atoms, benzoyl chloride, benzoyl bromide, 2-methylbenzoyl halides, 3-methylbenzoyl halides and 4-methylbenzoyl halides where halide is bromide or chloride, 2-furoyl

halide and 3-furoyl halide where halide is chloride or bromide, 2-thenoyl halide and 3-thenoyl halide where halide is chloride or bromide, allyl halide and 2-methylallyl halide where halide is bromide or chloride. In the aforesaid reaction, at least a molar equivalent amount of the halide, and preferably an excess to ensure complete reaction, is added to a solution of the quinazoline in an organic solvent such as a methyl alkyl ketone, saturated aliphatic hydrocarbon or alkanol at room temperature. The reaction mixture is stirred for at least 1/2 hour and up to about 5 hours, depending, of course, on the size of the sample. While higher reaction times may be used they result in noxious fumes. Lower temperatures require longer periods of time for the compounds to react. The solid product is filtered from the reaction mixture and the product may be recrystallized from such solvents as methanol, ethanol, isopropanol, methylene chloride and chloroform.

In method (4) 2-aminobenzonitriles of the formula:

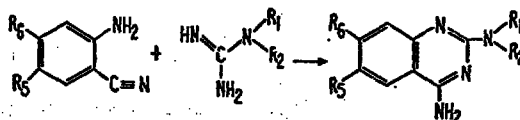


where R_5 and R_6 are as previously disclosed, are reacted with guanidines of the formulae:

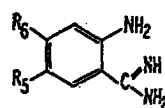
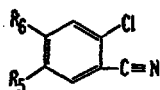


where R_1 , R_2 and Z are as previously disclosed. In this method, the benzonitrile is dissolved in an inert high-boiling solvent such as dimethylformamide, dimethyl sulfoxide or ethylene glycol. A molar equivalent amount and preferably an excess of the guanidine is added and the mixture is heated at about 150°C. for from about 4 to 15 hours.

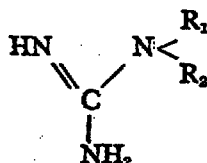
While lower temperatures may be employed for longer periods of time, about 12 hours are preferable for 0.1 molar quantities of reactants to ensure complete reaction. After heating, the solution is concentrated *in vacuo* to a small volume, water is added, and the mixture is chilled. The solids which precipitate are filtered from the mixture and recrystallized from solvents such as methanol-water, and dried. The reaction is illustrated as follows:



In methods (5) and (6), the compounds of this invention are prepared by reacting compounds of the formulae:

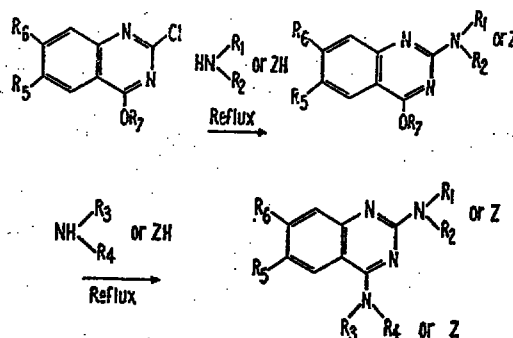


where R_5 and R_6 are as previously mentioned, with guanidines of the formula:



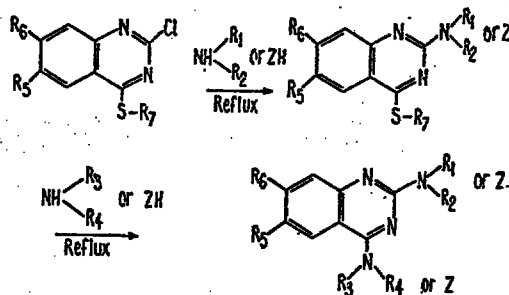
by the process described for method (4).

In method (7), 2-chloro-4-alkoxy-6- R_5 -7- R_6 -quinazolines whose preparation is described in Curd, Landquist and Rose, J. Chem. Soc., 1947, pages 775-783, are reacted at reflux with an amino compound in alcohol for several hours to obtain the 2-amino-4-alkoxy-6- R_5 -7- R_6 -quinazoline. The resulting compound is then reacted with the same or a different amino compound at higher temperatures to obtain substitution on that position. The reaction sequence is as follows:



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and Z are as previously mentioned and wherein R_7 is alkyl, preferably methyl or ethyl. In a further extension of this general procedure, the corresponding compounds having a 4-phenoxy or benzyloxy group may be employed.

In method (8), 2-chloro-4-alkylthio-6- R_5 -7- R_6 -quinazolines are reacted with amino compounds in refluxing alcohol to obtain 2,4-disubstituted-6- R_5 -7- R_6 -quinazolines. The reaction sequence is as follows:



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and Z are as previously disclosed.

It is obvious that when the final product formed has R_1 to R_4 as a labile hydrogen atom (or where Z is unalkylated) the product can be alkylated, aralkylated or alkenylated to replace the hydrogen atom by a group falling within the definition of R_1 to R_4 . Similarly, the Z group in the product can be subsequently alkanoylated or aroylated.

The compounds of this invention are administered to hypertensive subjects either alone or in combinations with pharmaceutically-acceptable carriers. The proportion of active ingredient to carrier is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they are administered in tablet form with such excipients as lactose, sodium citrate, calcium carbonate and dicalcium phosphate. Various disintegrants such as starch, alginic acid and certain complex silicates together with lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often used. For oral administration in capsule form, preferred materials are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are desired, the essential active ingredients are combined with emulsifying and/or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and various combinations of diluents are employed. For parenteral administration, solutions of the active ingredients in combination with other solutes such as glucose or saline are used. Such aqueous solutions should be suitably buffered if necessary to render them isotonic.

The dosage required to reduce blood pressure in hypertensive subjects will be

determined by the nature and the extent of the hypertension. Generally, small dosages will be administered initially with a gradual increase in dosage until the optimum level is determined. It will generally be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level of blood pressure reduction as produced by a smaller quantity administered parenterally. In general, from about 0.02 to 200 milligrams of active ingredient per kilogram of body weight administered in single or multiple dosage units effectively reduces blood pressure in hypertensive subjects. Tablets containing 20 to 250 milligrams of active ingredient are particularly useful.

The following examples are given by way of illustration and are not to be construed as limiting the invention in any way. Examples 1, 5, 6, 7, 8, 11, 12, 14, 16 and 64 hereinafter relates to the preparation of intermediates for use in the preparation of compounds of the invention.

EXAMPLE 1.

2-Chloro-4-Amino-6,7-Dimethoxyquinazoline

To 800 ml. of a solution of anhydrous ammonia in tetrahydrofuran at room temperature are added 30 g. of 2,4-dichloro-6,7-dimethoxyquinazoline [F. H. S. Curd et. al., J. Chem. Soc., p. 1759 (1948)]. The mixture is stirred for 44 hours. The precipitate (29 g. m.p. 267—268°C.) is filtered and recrystallized from methanol to yield 19 g. of 2-chloro-4-amino-6,7-dimethoxyquinazoline, m.p. 302°C. (dec.).

Anal. Calcd. for $C_{10}H_{10}N_2O_2Cl$: C, 50.11; H, 4.20; N, 17.53; Cl, 14.79.
Found: C, 49.99; H, 4.27; N, 17.52; Cl, 14.82.

EXAMPLE 2.

2,4-Di-(N,N-Diphenylamino)-6,7-Dimethoxyquinazoline

To a pressure bottle are added 7.78 g. of 2,4-dichloro-6,7-dimethoxyquinazoline in 100 ml. of a 25% solution of diphenylamine in ethanol. The mixture is heated at 160°C. for 65 hours. The clear solution is evaporated to dryness and the residue is recrystallized from dimethylformamide/water to yield the product. The product is dissolved in 400 ml. of hot water. The solution is made alkaline with sodium bicarbonate and the resulting precipitate is filtered, washed with water and dried to yield 2,4-di-(N,N-diphenylamino)-6,7-dimethoxyquinazoline.

EXAMPLE 3.

2-(N,N-Dibenzylamino)-4-(N,N-Diethylamino)-6,7-Dimethoxyquinazoline

To 800 ml. of a solution of diethylamine in tetrahydrofuran at room temperature are added 30 g. of 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred for 48 hours. The precipitate is filtered and recrystallized from methanol. To 5 grams of the product is added a 25% solution of dibenzylamine in ethanol. The mixture is heated at 160°C. for 16 hours in a pressure bottle. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE 4

A number of 2,4-disubstituted-6,7-dimethoxyquinazolines are prepared in the same manner as Examples 2 and 3 from 2,4-dichloro-6,7-dimethoxyquinazoline and the appropriate amino compound. The products of these reactions are given in Table II.

EXAMPLE 5

2,4-Dichloro-6-Methoxy-7-Amyloxyquinazoline

To 20 grams of 4-amyoxy-5-methoxy anthranilic acid amide in acetic acid (100 ml.) is added a suspension of sodium cyanate (11 g.) in water (50 gml.) and the mixture is stirred well. After 1 hour, 2-ureido-4-amyoxy-5-methoxy benzamide is collected, washed and recrystallized from water. Twenty grams of the product are heated with 8N hydrochloric acid (50 ml.) on a steam bath for 1 hour. The resulting product is stirred with 35% aqueous sodium hydroxide (50 ml.) to form the sodium salt. The salt is filtered, redissolved in 500 ml. hot water and re-precipitated with acetic acid to give 2,4-dihydroxy-6-methoxy-7-amyoxyquinazoline. The product is dried and converted to 2,4-dichloro-compound by refluxing 10 grams of the dihydroxy material with 16 g. phosphorus pentachloride and 10 ml. phosphoryl chloride for several hours. After removal of the phosphoryl chloride, the product is distilled from the flask under reduced pressure.



EXAMPLE 6

2,4-Dichloro-6-Amyloxy-7-Methoxyquinazoline

This compound is prepared from 4-methoxy-5-amyoxyanthranilic acid according to the procedure of Example 5.

EXAMPLE 7

2,4-Dichloro-6,7-Diamyloxyquinazoline

To 20 grams of 4,5-diamyloxyanthranilamide in acetic acid (100 cc) is added a suspension of 11 g. sodium cyanate in 50 ml. water and the mixture is stirred well. After 1 hour, 2-ureido-4,5-diamyloxybenzamide is collected, washed and recrystallized from water. Twenty grams of the product are heated with 8N hydrochloric acid (45 cc) on a steam bath for 1 hour. The resulting product is stirred with 35% sodium hydroxide (50 cc) to form the sodium salt. The salt is filtered, redissolved in 500 cc hot water and reprecipitated with acetic acid to give 2,4-dihydroxy-6,7-diamyloxyquinazoline. The product is dried and converted to 2,4-dichloro-6,7-diamyloxyquinazoline by refluxing 10 grams of dihydroxy compound with 16 g. phosphorous pentachloride and 10 cc phosphoryl chloride for six hours. After removal of the phosphoryl chloride, the product is distilled from the flask under reduced pressure.

EXAMPLE 8

2,4-Dichloro-6,7-Diethoxyquinazoline

2,4-Dichloro-6,7-diethoxyquinazoline is prepared by the procedure of Example 7 starting with 4,5-diethoxyanthranilamide, 4,5-diethoxyanthranilic acid or an alkyl ester of 4,5-diethoxyanthranilic acid such as methyl 4,5-diethoxyanthranilate.

EXAMPLE 9

2,4-Disubstituted-6,7-diamyloxyquinazolines are prepared from 2,4-dichloro-6,7-diamyloxyquinazoline by the procedures of Examples 2 and 3. These compounds are listed in Table II.

EXAMPLE 10

A 2,4-disubstituted-6,7-diethoxyquinazoline is prepared from 2,4-dichloro-6,7-diethoxyquinazoline according to the procedure of Example 3. This compound is listed in Table II.

EXAMPLE 11

2,4-Dichloro-6-Methoxyquinazoline

2,4-Dichloro-6-methoxyquinazoline is prepared by the procedure of Example 5 from 5-methoxyanthranilic acid, 5-methoxyanthranilamide or an alkyl ester of 5-methoxyanthranilic acid such as methyl 5-methoxyanthranilate.

EXAMPLE 12

2,4-Dichloro-7-Methoxyquinazoline

2,4-Dichloro-7-methoxyquinazoline is prepared from 4-methoxyanthranilamide, 4-methoxyanthranilic acid or an alkyl ester of the acid according to the procedure of Example 5.

EXAMPLE 13

2,4-Disubstituted-6-Methoxyquinazolines and 2,4-Disubstituted-7-Methoxyquinazolines

A number of 2,4-disubstituted 6- and 7-methoxyquinazolines are prepared according to the procedures of Examples 2 and 3. These compounds are listed in Table II.

EXAMPLE 14

2,4-Dichloro-6-(7)-Amyloxyquinazoline

2,4-Dichloro-6-amyoxyquinazoline and 2,4-dichloro-7-amyoxyquinazoline are prepared according to the procedure of Example 5 from 5-amyoxyanthranilamide and 4-amyoxyanthranilamide, respectively, or the corresponding acids and alkyl esters.

EXAMPLE 15

2,4-Disubstituted-7-Amyloxyquinazoline

2,4-Disubstituted-7-amyoxyquinazolines are prepared from the corresponding dichloro-compounds according to the procedures of Examples 2 and 3. These compounds are listed in Table II.

EXAMPLE 16

2,4-Dichloro-6-Methoxy-7-Amyloxyquinazoline

2,4-Dichloro-6-methoxy-7-amyoxyquinazoline is prepared by the procedure of Example 5 with 4-amyoxy-5-methoxyanthranilamide or 4-amyoxy-5-methoxyanthranilic acid or its alkyl esters.

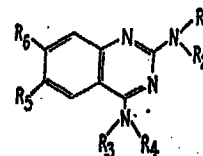
xordng 5
 ided a 10
 d well. 10
 alized 10
 c acid 10
 1.35% 10
 lved in 10
 ry-6,7- 10
 6,7-di- 10
 phos- 10
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 nple 7 20
 l ester 20
 ro-6,7- 25
 ds are 25
 ro-6,7- 30
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 com- 55
 ure of 60
 thoxy- 60

EXAMPLE 17

2,4-Disubstituted-6-Methoxy-7-amyloxyquinazoline

A 2,4-disubstituted-6-methoxy-7-amyloxyquinazoline is prepared by the procedure of Example 2. This compound is listed in Table II which illustrates compounds of the present invention including compounds prepared in the foregoing Examples.

TABLE II



R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
CH ₂ =CH-CH ₂ -	CH ₂ =CH-CH ₂ -	CH ₂ =CH-CH ₂ -	CH ₂ =CH-CH ₂ -	CH ₃ O-	CH ₃ O-
CH ₂ =CH-(CH ₂) ₃ -	CH ₂ =CH-(CH ₂) ₃ -	CH ₂ =CH-(CH ₂) ₃ -	CH ₂ =CH-(CH ₂) ₃ -	CH ₃ O-	CH ₃ O-
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -	C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -	CH ₃ O-	CH ₃ O-
2-OH-C ₆ H ₄ -	C ₆ H ₅ -	C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -	CH ₃ O-	H-
4-Cl-C ₆ H ₄ -	2-HO-CH ₂ -	C ₆ H ₅ -CH ₂ -	2-HO-CH ₂ -	CH ₃ O-	CH ₃ O-
2-CH ₃ O-C ₆ H ₄ -	C ₆ H ₅ -	2-CH ₃ O-C ₆ H ₄ -	C ₆ H ₅ -	H-	CH ₃ O-
C ₆ H ₅ -	C ₆ H ₅ -	C ₆ H ₅ -	C ₆ H ₅ -	CH ₃ O-	H-
C ₆ H ₅ -	H-	C ₆ H ₅ -	H-	H-	CH ₃ O-
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	H-	H-	C ₂ H ₅ O-	C ₂ H ₅ O-
4-Cl-C ₆ H ₄ -	H-	4-Cl-C ₆ H ₄ -	H-	C ₂ H ₅ O-	H-
3,4-Cl ₂ -C ₆ H ₃ -	H-	H-	H-	C ₃ H ₇ O-	C ₃ H ₇ O-
3-Br-C ₆ H ₄ -	3-Br-C ₆ H ₄ -	H-	H-	C ₃ H ₇ O-	C ₃ H ₇ O-
2-OH-C ₆ H ₄ -	H-	2-OH-C ₆ H ₄ -	H-	C ₄ H ₉ O-	H-

TABLE II (Continued)

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
HO-CH ₂ -	HO-CH ₂ -	H-	H-	C ₄ H ₉ O-	C ₄ H ₉ O-
HO-(CH ₂) ₅ -	HO-(CH ₂) ₅ -	HO-(CH ₂) ₅ -	H-	H-	C ₅ H ₁₁ O-
2-CH ₃ O-C ₆ H ₄ -	H-	2-CH ₃ O-C ₆ H ₄ -	H-	C ₆ H ₁₁ O-	C ₅ H ₁₁ O-
3-CH ₃ O-C ₆ H ₄ -	3-CH ₃ O-C ₆ H ₄ -	H-	H-	H-	C ₅ H ₁₁ O-
2-C(F) ₃ CH ₂ -	H-	H-	H-	CH ₃ O-	CH ₃ O-
2-C(F) ₃ -CH ₂ -	H-	H-	H-	C ₂ H ₅ O-	CH ₃ O-
4-(C ₆ H ₁₃ O)-C ₆ H ₄ -	4-(C ₆ H ₁₃ O)-C ₆ H ₄ -	H-	H-	C ₃ H ₁₁ O-	C ₆ H ₁₁ O-
2,4-(CH ₃) ₂ -C ₆ H ₃ -	H-	2,4-(CH ₃) ₂ -C ₆ H ₃ -	H-	CH ₃ O-	C ₆ H ₁₁ O-
2,4-(C ₆ H ₁₃)-C ₆ H ₃ -	2,4-(C ₆ H ₁₃)-C ₆ H ₃ -	H-	H-	CH ₃ O-	C ₂ H ₅ O-
2-(C ₆ H ₁₃)C ₆ H ₄ -	H-	2-(C ₆ H ₁₃)-C ₆ H ₄ -	H-	C ₅ H ₁₁ O-	CH ₃ O-
2,4-Br ₂ C ₆ H ₃ -	2,4-Br ₂ C ₆ H ₃ -	H-	H-	C ₂ H ₅ O-	CH ₃ O-
2-CH ₃ -C ₆ H ₄ -	H-	2-CH ₃ -C ₆ H ₄ -	H-	H-	C ₂ H ₅ O-
3-CH ₃ -C ₆ H ₄ -	3-CH ₃ -C ₆ H ₄ -	2-CH ₃ -C ₆ H ₄ -	H-	H-	CH ₃ O
C ₆ H ₅ -	H-	C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	CH ₃ O-	C ₂ H ₅ O-
5-Cl-C ₆ H ₅ -	3-Cl-C ₆ H ₅ -	HO-CH ₂ -	H-	H-	C ₃ H ₇ O-
2-HO-C ₆ H ₄ -	H-	2-HO-C ₆ H ₄ -	H-	H-	C ₅ H ₁₁ O-
2-F-C ₆ H ₄ -	H-	2,4-F ₂ -C ₆ H ₃ -	H-	CH ₃ O-	CH ₃ O-
3-F-C ₆ H ₄ -	3-F-C ₆ H ₄ -	3-F-C ₆ H ₄ -	3-F-C ₆ H ₄ -	CH ₃ O-	CH ₃ O-
H-	H-	H-	H-	CH ₃ O-	CH ₃ O-
C ₆ H ₅ -C ₂ H ₄ -	C ₆ H ₅ -C ₂ H ₄ -	C ₆ H ₅ -C ₂ H ₄ -	C ₆ H ₅ -C ₂ H ₄ -	CH ₃ O-	H-

EXAMPLE 18

To 80 ml. of a 25% solution of morpholine in tetrahydrofuran at room temperature are added 30 g. 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred for 48 hours. The precipitate is filtered and recrystallized from methanol. To 5 g. of the product are added 100 ml. of ethanolic ammonia. The mixture is heated at 160°C. for 16 hours in a pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water. The compound produced is 2-amino-4-morpholino-6,7-dimethoxyquinazoline.

EXAMPLE 19

A 2-aminoquinazoline is prepared from 2,4-dichloro-6,7-dimethoxyquinazoline according to the procedure of Example 18. This compound is listed in Table III.

EXAMPLE 20

2-Dimethylamino-4-Morpholino-6,7-Dimethoxyquinazoline

To 80 ml. of a 25% solution of morpholine in tetrahydrofuran at room temperature are added 30 g. 2,4-dichloro-6,7-dimethoxyquinazoline prepared by the procedure described in Example I. The mixture is stirred for 48 hours. The precipitate is filtered off and recrystallized from methanol. To 5 g. of the product are added 12 grams of a 25% solution of dimethylamine in ethanol. The mixture is heated at 160°C. for 16 hours in a pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE 21

2,4-Disubstituted-6,7-dimethoxyquinazolines are prepared according to the procedure of Example 20. These compounds are listed in Table III.

EXAMPLE 22

2-Amino-4-Morpholino-6-Methoxy-7-Amyloxyquinazoline

This compound is prepared from 2,4-dichloro-6-methoxy-7-amlyoxyquinazoline according to the procedure of Example 18. The dihydrochloride salt is prepared from the base compound according to the procedure of Example 24.

EXAMPLE 23

2-Amino-4-substituted-6-methoxy-7-amlyoxyquinazolines are prepared according to the procedure of Example 22 substituting the appropriate amino compound for morpholine in the procedure.

EXAMPLE 24

2-Amino-4-substituted-6(7)methoxyquinazolines and the 2,4-disubstituted-6(7)-methoxyquinazolines are prepared according to the procedures of Examples 12 and 18. The dihydrochloride salts are prepared by dissolving the bases in hot ethanol and adding an ethanolic hydrochloric acid solution to precipitate the salt. These compounds are listed in Table III.

EXAMPLE 25

2,4-Disubstituted-6(7)amyloxyquinazolines and the 2-amino-4-substituted 6(7)-amyloxyquinazolines are prepared according to the procedures of Examples 18 and 20. The dihydrochloride salts are prepared according to the procedure of Example 24.

EXAMPLE 26

2,4-Disubstituted-6(7)ethoxyquinazolines and the 2-amino-4-substituted-6(7)-ethoxyquinazolines are prepared from 4-ethoxyanthranilic acid and 5-ethoxyanthranilic acid, and their amides and alkyl esters according to the above procedures. The dihydrochloride salts are prepared according to the procedure of Example 24. The following Table illustrates compounds of the present invention including compounds prepared in the foregoing Examples.

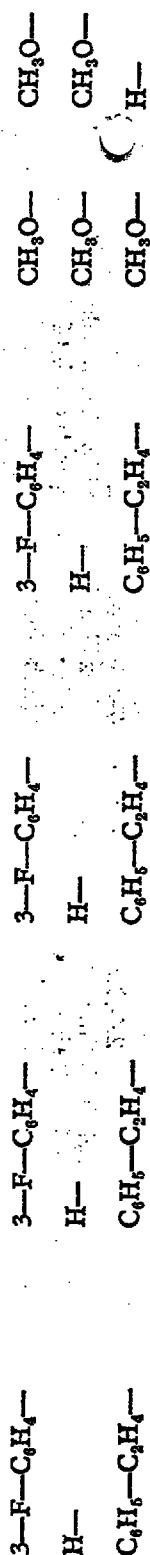
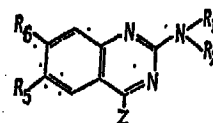


TABLE III



R ₁	R ₂	Z	R ₅	R ₆
H—	H—	piperidino-	CH ₃ O—	CH ₃ O—
H—	H—	4-methyl-1-piperaziny-	CH ₃ O—	H—
H—	H—	4-pentyl-1-piperaziny-	H—	CH ₃ O—
CH ₂ =CH—CH ₂ —	CH ₂ =CH—CH ₂ —	4-hydroxymethyl-1-piperaziny-	C ₂ H ₅ O—	C ₂ H ₅ O—
CH ₂ =CH—(CH ₂) ₃ —	CH ₂ =CH—(CH ₂) ₃ —	morpholino-	H—	C ₂ H ₅ O—
C ₆ H ₅ —	C ₆ H ₅ —	2,6-dimethylmorpholino-	C ₂ H ₅ O—	H—
C ₆ H ₅ —	H—	2,6-dipentylmorpholino-	C ₃ H ₇ O—	C ₃ H ₇ O
C ₆ H ₅ —C ₂ H ₄ —	C ₆ H ₅ —C ₂ H ₄ —	3-oxo-1-piperaziny-	C ₃ H ₇ O	H—
2—Cl—C ₆ H ₄ —	2—Cl—C ₆ H ₄ —	4-acetyl-1-piperaziny-	H—	C ₃ H ₇ O—
3—Cl—C ₆ H ₄ —	H—	4-phenyl-1-piperaziny-	C ₄ H ₉ O—	C ₄ H ₉ O—
4—Cl—C ₆ H ₄ —	4—Cl—C ₆ H ₄ —	1-pyrrolidiny-	H—	C ₄ H ₉ O—
C ₆ H ₅ —	C ₆ H ₅ —	cyclopropylamino	H—	C ₃ H ₇ O—
2—Cl—C ₆ H ₄ —	H—	cyclobutylamino	C ₂ H ₅ O—	C ₂ H ₅ O—
CH ₂ =CH—CH ₂ —	H—	cycloheptylamino	C ₃ H ₇ O—	C ₃ H ₇ O—
2—Br—C ₆ H ₄ —	2—Br—C ₆ H ₄ —	4-valeryl-1-piperaziny-	C ₄ H ₉ O—	H—
3—Br—C ₆ H ₄ —	H—	4-valeryl-1-piperaziny-	C ₅ H ₁₁ O—	C ₅ H ₁₁ O—

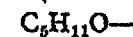
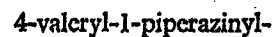
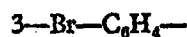
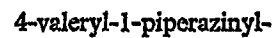


TABLE III—continued

R ₁	R ₂	Z	R ₅	R ₆
2-F-C ₆ H ₄ -	2-F-C ₆ H ₄ -	1-pyrrolidinyl-	H-	C ₆ H ₁₁ O-
2,4-Cl ₂ C ₆ H ₃ -	2,4-Cl ₂ -C ₆ H ₃ -	piperidino-	C ₆ H ₁₁ O-	H-
4-Br-C ₆ H ₄ -	4-Br-C ₆ H ₄ -	piperidino-	CH ₃ O-	CH ₃ O-
2-HO-C ₆ H ₄ -	2-HO-C ₆ H ₄ -	4-methyl-piperazinyl-1-	CH ₃ O-	CH ₃ O-
3-HO-C ₆ H ₄ -	H-	4-pentyl-piperazinyl-1-	CH ₃ O-	H-
4-HO-C ₆ H ₄ -	H-	4-hydroxymethylpiperazinyl-1-	H-	CH ₃ O-
HO-CH ₂ -	H-	morpholino-	C ₂ H ₅ O-	C ₂ H ₅ O-
HO-CH ₂ -(CH ₂) ₄ -	HO-CH ₂ -(CH ₂) ₄ -	2,6-dimethylmorpholino	H-	C ₂ H ₅ O-
2-CH ₃ -C ₆ H ₄ -	2-CH ₃ -C ₆ H ₄ -	2,6-dipentylmorpholino	C ₃ H ₇ O-	C ₃ H ₇ O-
3-CH ₃ -C ₆ H ₄ -	H-	4-benzoyl-1-piperazinyl	C ₆ H ₁₁ O-	H-
4-CH ₃ -C ₆ H ₄ -	H-	morpholino-	CH ₃ O-	C ₆ H ₁₁ O-
2,6-(CH ₃) ₂ C ₆ H ₃ -	H-	1-azacyloheptyl-	C ₆ H ₁₁ O-	CH ₃ O-
2-CH ₃ O-C ₆ H ₄ -	2-CH ₃ O-C ₆ H ₄ -	1-azacylooctyl-	C ₂ H ₅ O-	CH ₃ O-
3-CH ₃ O-C ₆ H ₄ -	3-CH ₃ O-C ₆ H ₄ -	1-piperazinyl-	C ₃ H ₇ O-	C ₆ H ₁₁ O-

TABLE III—continued

R_1	R_2	Z	R_5	R_6
4-CH ₃ O-C ₆ H ₄ -	H-	1-piperazinyl-	CH ₃ O-	H-
2-C ₆ H ₁₃ O-C ₆ H ₄ -	H-	3-oxo-1-piperazinyl-	H-	CH ₃ O-
3-C ₆ H ₁₃ O-C ₆ H ₄ -	H-	4-acetyl-1-piperazinyl-	H-	C ₅ H ₁₁ O-
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	piperidino-	CH ₃ O-	CH ₃ O-
CH ₂ =CH-CH ₂ -	C ₆ H ₅ -	piperidino-	C ₂ H ₅ O-	H-
2-Cl-C ₆ H ₄ -	C ₆ H ₅ -	1-pyrrolidinyl-	H-	CH ₃ O-
4-HO-C ₆ H ₄ -	3-CH ₃ O-C ₆ H ₄ -	morpholino-	H-	CH ₃ O-
HO-CH ₂ -	C ₆ H ₅ -CH ₂ -	morpholino-	C ₂ H ₅ O-	C ₂ H ₅ O-
2-C ₆ H ₁₃ -C ₆ H ₅ -	H-	1-piperazinyl-	H-	CH ₃ O-
3-F-C ₆ H ₄ -	H-	morpholino-	CH ₃ O-	C ₅ H ₁₁ O-
4-F-C ₆ H ₄ -	H-	2,6-dimethylmorpholino-	CH ₃ O-	C ₂ H ₅ O-
4-F-C ₆ H ₄ -	4-F-C ₆ H ₄ -	1-pyrrolidinyl-	CH ₃ O-	H-
3-C ₆ H ₁₃ -C ₆ H ₄ -	H-	1-pyrrolidinyl-	C ₅ H ₁₁ O-	C ₂ H ₅ O-
4-C ₆ H ₁₃ -C ₆ H ₄ -	4-C ₆ H ₁₃ -C ₆ H ₄ -	1-pyrrolidinyl-	H-	C ₂ H ₅ O-

EXAMPLE 27

2-(4-Methyl-1-piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline

To 5 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline prepared as in Example I, are added 20 grams of a 25% solution of 4-methylpiperazine in ethanol. The mixture is heated at 160°C. for 16 hours in a pressure bottle. The solvent is then evaporated and the residue is recrystallized from methanol/water.

EXAMPLE 28

2-Morpholino-4-(N,N-Dibenzylamino)-6,7-Diamyloxyquinazoline

To 30 grams 2,4-dichloro-6,7-diamyloxyquinazoline prepared as in Example 7 are added 100 ml. of a 10% solution of dibenzylamine in tetrahydrofuran at room temperature. The mixture is stirred for 48 hours. The resulting precipitate is filtered and recrystallized from methanol. To 5 grams of the product are added 50 ml. of a 25% solution of morpholine in ethanol. The mixture is heated at 160°C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE 29

2-Substituted-4-amino-6,7-dimethoxyquinazolines are prepared as in Example 27. The dihydrochloride salts are prepared according to the procedure of Example 24.

EXAMPLE 30

2,4-Disubstituted-6,7-dimethoxyquinazolines where the 2-carbon atom is substituted with a heterocyclic nitrogen compound, are prepared as in Example 28. These compounds are listed in Table IV.

EXAMPLE 31

2,4-Disubstituted-6,7-diamyloxyquinazolines are prepared as in Example 28 from 2,4-dichloro-6,7-diamyloxyquinazoline. The dihydrochloride salts are prepared as in Example 24. These compounds are listed in Table IV.

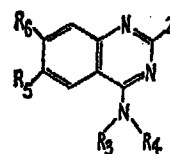
EXAMPLE 32

2,4-Disubstituted-6-methoxy-7-amyloxyquinazolines are prepared from 2,4-dichloro-6-methoxy-7-amyloxyquinazoline according to the procedure of Example 28. Pharmaceutically-acceptable acid addition salts of these compounds are prepared according to the procedure of Example 24, employing the appropriate acid. These compounds are listed in Table IV.

EXAMPLE 33

2,4-Disubstituted-6(7)methoxyquinazolines are prepared from 2,4-dichloro-6-methoxyquinazoline and 2,4-dichloro-7-methoxyquinazoline according to the procedure of Example 28. Pharmaceutically-acceptable acid addition salts of these compounds are prepared according to the procedure of Example 24, employing the appropriate acid. The compounds are listed in Table IV. Table IV illustrates compounds of the present invention including compounds prepared in the foregoing Examples.

TABLE IV



R ₃	R ₄	Z	R ₅	R ₆
H—	C ₆ H ₅	4-alkyl-1-piperazinyl-	CH ₃ O—	CH ₃ O
H—	H—	2,6-dipentylmorpholino-	C ₅ H ₁₁ O—	C ₅ H ₁₁ O—
CH ₂ =CH—CH ₂ —	CH ₂ =CH—CH ₂ —	2,6-dimethylmorpholino-	C ₅ H ₁₁ O—	CH ₃ O—
CH ₂ =CH—(CH ₂) ₃ —	H—	1-pyrrolidinyl-	C ₅ H ₁₁ O—	C ₂ H ₅ O—
C ₆ H ₅ —	C ₆ H ₅ —	morpholino-	C ₅ H ₁₁ O—	C ₃ H ₇ O—
C ₆ H ₅ —	H—	4-hydroxymethyl-1-piperazinyl-	C ₄ H ₉ O—	C ₄ H ₉ O—
HO—CH ₂ —	HO—CH ₂ —	piperidino-	C ₅ H ₁₁ O—	C ₄ H ₉ O—
HO—CH ₂ —	H—	4-hydroxypentyl-1-piperazinyl	CH ₃ O—	H—
HO—(CH ₂) ₅ —	HO—(CH ₂) ₅ —	morpholino-	CH ₃ O—	C ₂ H ₅ O—
HO—(CH ₂) ₆ —	H—	1-azacycloheptyl-	CH ₃ O—	C ₃ H ₇ O—
2—CH ₃ O—C ₆ H ₄ —	2—CH ₃ O—C ₆ H ₄ —	1-azacyclooctyl-	H—	C ₃ H ₇ O—
2—CH ₃ O—C ₆ H ₄ —	H—	4-phenyl-1-piperazinyl-	H—	C ₅ H ₁₁ O—
3—CH ₃ O—C ₆ H ₄ —	H—	4-methyl-1-piperazinyl-	C ₂ H ₅ O—	H—
4—CH ₃ O—C ₆ H ₄ —	4—CH ₃ O—C ₆ H ₄	4-pentyl-1-piperazinyl-	C ₂ H ₅ O—	H—
4—CH ₃ O—C ₆ H ₄ —	H—	3-oxo-1-piperazinyl	CH ₃ O—	CH ₃ O—
C ₆ H ₅ —CH ₂ —	C ₆ H ₅ —	morpholino-	CH ₃ O—	C ₂ H ₅ O—

4-CH ₃ O-C ₆ H ₄ -	4-CH ₃ O-C ₆ H ₄ -	4-pentyl-1-piperazinyl-	C ₂ H ₅ O-	H-
4-CH ₃ O-C ₆ H ₄ -	H-	3-oxo-1-piperazinyl	CH ₃ O-	CH ₃ O-
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -	morpholino-	CH ₃ O-	C ₂ H ₅ O-

TABLE IV—continued

R ₃	R ₄	Z	R ₅	R ₆
4-CH ₃ O-C ₆ H ₄ -	C ₆ H ₅ -	morpholino-	CH ₃ O-	C ₅ H ₁₁ O-
3-Br-C ₆ H ₄ -	C ₆ H ₅ -	1-pyrrolidinyl-	CH ₃ O-	CH ₃ O-
2-CH ₃ O-C ₆ H ₄ -	HO-(CH ₂) ₅ -	piperidino-	H-	CH ₃ O-
HO-CH ₂ -	C ₆ H ₅ -CH ₂ -	1-pyrrolidinyl-	H-	CH ₃ O-
HO-CH ₂ -	C ₆ H ₅ -CH ₂ -	cyclopropylamino	H-	C ₃ H ₇ O-
HO-CH ₂ -	HO-CH ₂ -	cycloheptylamino	CH ₃ O-	CH ₃ O-
C ₆ H ₅ -	C ₆ H ₅ -	cyclohexylamino	CH ₃ O-	CH ₃ O-
2-C ₆ H ₁₃ -C ₆ H ₄ -	2-C ₆ H ₁₃ -C ₆ H ₄ -	morpholino-	CH ₃ O-	CH ₃ O-
3-C ₆ H ₁₃ -C ₆ H ₄ -	H-	piperidino-	H-	CH ₃ O-
4-C ₆ H ₁₃ -C ₆ H ₄ -	4-C ₆ H ₁₃ -C ₆ H ₄ -	4-methyl-1-piperazinyl-	CH ₃ O-	H-
2-Cl-C ₆ H ₄ -	2-Cl-C ₆ H ₄ -	4-pentyl-1-piperazinyl-	C ₂ H ₅ O-	C ₂ H ₅ O-
2-Cl-C ₆ H ₄ -	H-	4-phenyl-1-piperazinyl	H-	C ₂ H ₅ O-
3-Cl-C ₆ H ₄ -	H-	3-oxo-1-piperazinyl-	C ₂ H ₅ O-	H-
4-Cl-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	4-acetyl-1-piperazinyl-	C ₅ H ₁₁ O-	C ₅ H ₁₁ O-
2-Br-C ₆ H ₄ -	H-	4-n-valeryl-1-piperazinyl-	H-	C ₅ H ₁₁ O-
3-Br-C ₆ H ₄ -	H-	4-benzoyl-1-piperazinyl-	C ₅ H ₁₁ O-	H-
4-Br-C ₆ H ₄ -	4-Br-C ₆ H ₄ -	2,6-dimethylmorpholino-	CH ₃ O-	C ₅ H ₁₁ O-

TABLE IV—continued

R ₃	R ₄	Z	R ₅	R ₆
2-F-C ₆ H ₄ —	2-F-C ₆ H ₄ —	2,6-dipentylmorpholino-	C ₅ H ₁₁ O—	CH ₃ O—
3-F-C ₆ H ₄ —	H—	1-azacycloheptyl-	C ₂ H ₅ O—	CH ₃ O—
4-F-C ₆ H ₄ —	4-F-C ₆ H ₄ —	1-azacylooctyl-	C ₂ H ₅ O—	C ₅ HO ₁₁ —
2-C(F ₃)—CH ₂ —	H—	1-pyrrolidiny-	CH ₃ O—	CH ₃ O—
2-C ₆ H ₁₃ O—C ₆ H ₄ —	H—	piperidino	CH ₃ O—	H—
3-C ₆ H ₁₃ O—C ₆ H ₄ —	H—	4-methyl-1-piperaziny-	CH ₃ O—	CH ₃ O—
4-C ₆ H ₁₃ O—C ₆ H ₄ —	4-C ₆ H ₁₃ O—C ₆ H ₄ —	1-pyrrolidiny-	C ₂ H ₅ O—	H—
C ₆ H ₅ —CH ₂ —	C ₆ H ₅ —CH ₂ —	4-pentyl-1-piperaziny-	C ₂ H ₅ O—	C ₂ H ₅ O—
C ₆ H ₅ —CH ₂ —	H—	morpholino-	H—	CH ₃ O—
C ₆ H ₅ —CH ₂ —CH ₂ —	C ₆ H ₅ —CH ₂ —CH ₂ —	4-n-valeryl-1-piperaziny-	H—	C ₂ H ₅ O—
C ₆ H ₅ —CH ₂ —	H—	4-acetyl-1-piperaziny-	H—	C ₅ H ₁₁ O—
2-CH ₃ —C ₆ H ₄ —	2-CH ₃ —C ₆ H ₄ —	3-oxo-1-piperaziny-	C ₅ H ₁₁ O—	C ₅ H ₁₁ O—
2-CH ₃ —C ₆ H ₄ —	H—	4-benzoyl-1-piperaziny-	C ₅ H ₁₁ O—	H—
3-CH ₃ —C ₆ H ₄ —	H—	4-phenyl-1-piperaziny-	C ₅ H ₁₁ O—	CH ₃ O—
4-CH ₃ —C ₆ H ₄ —	4-CH ₃ —C ₆ H ₄ —	1-azacycloheptyl-	CH ₃ O—	C ₅ H ₁₁ O—
2,6-(CH ₃) ₂ —C ₆ H ₃ —	H—	1-azacyclooctyl-	CH ₃ O—	C ₂ H ₅ O—

22

EXAMPLE 34

2-(N,N-Diethylamino)-4-Amino-6,7-Dimethoxyquinazoline

To 5 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline are added 50 ml. of a 25% solution of diethylamine in ethanol. The mixture is heated for 16 hours at 160°C. in a pressure bottle. The solvent is evaporated and the residue (6.9 g.) is crystallized from methanol/water to yield 3.3 grams of product melting at 179—180°C.

Anal. Calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28.
Found: C, 61.07; H, 7.17; N, 20.31.

EXAMPLE 35

2-(N,N-Diethylamino)-4-Amino-6,7-Dimethoxyquinazoline
Dihydrochloride

The dihydrochloride is prepared by dissolving the base in hot ethanol and adding ethanolic hydrochloric acid solution to precipitate the salt. M.P. 259—260°C.

EXAMPLE 36

2-(N,N-Diallylamino)-4-Amino-6,7-Dimethoxyquinazoline

The compound is prepared by the procedure of Example 34, using diallylamine in ethanol rather than diethylamine. The product melts 177—179°C. The dihydrochloride salt, prepared as in Example 36, melts 227—229°C.

EXAMPLE 37

2-Amino-4-(N,N-Dimethylamino)-6,7-Dimethoxyquinazoline

To 80 grams of a 10% solution of dimethylamine in tetrahydrofuran at room temperature are added 30 grams 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred for 48 hours. The resulting precipitate is filtered off and recrystallized from methanol. To 5 grams of the product are added 100 ml. of ethanolic ammonia. This mixture is heated at 160°C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE 38

2-Amino-4-(N,N-Diamylamino)-6,7-Diamyloxyquinazoline

To 30 grams of 2,4-dichloro-6,7-diamyloxyquinazoline, prepared as in Example 7, are added 80 grams of a 10% solution of diamylamine in tetrahydrofuran. The mixture is stirred for 48 hours. The precipitate which forms is filtered off and recrystallized from methanol. To 5 grams of the product are added 100 ml. ethanolic ammonia. This mixture is heated at 160°C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE 39

2,4-Di(N,N-Dimethylamino)-6,7-Dimethoxyquinazoline

To 80 grams of a 10% solution of dimethylamine in tetrahydrofuran at room temperature are added 30 grams 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred 48 hours. The resulting precipitate is filtered off and recrystallized from methanol. To 5 grams of the product are added 20 grams of a 10% solution of dimethylamine in ethanol. The mixture is heated in a sealed pressure bottle at 160°C. for 16 hours. The solvent is evaporated and the residue is recrystallized from methanol/water. The product melts at 121—122°C. The hydrochloride melts at 243°C.

Anal. Calcd. for $C_{14}H_{20}O_2N_2 \cdot HCl$:
C, 53.76; H, 6.76; N, 17.91; Cl, 11.33. Found:
C, 53.42; H, 6.71; N, 17.84; Cl, 11.16.

EXAMPLE 40

2,4-Di(N,N-Diamylamino)-6,7-Dimethoxyquinazoline

This compound is prepared from diarylamine according to the procedure of Example 39.

EXAMPLE 41

2,4-Di(N,N-Dimethylamino)-6,7-Methoxyquinazolines

These compounds are prepared from 2,4-dichloro-6-methoxyquinazoline (Example 11) and 2,4-dichloro-7-methoxyquinazoline (Example 12) according to the procedure of Example 39.



EXAMPLE 42

2-Methylamino-4-Amino-6,7-Dimethoxyquinazoline

This compound is prepared by the procedure of Example 34 by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with an ethanolic solution of methylamine.

5

EXAMPLE 43

2-Amylamino-4-Amino-6,7-Dimethoxyquinazoline

This compound is prepared by the procedure of Example 34 by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with an ethanolic solution of amylamine.

5

EXAMPLE 44

2-N-Ethylanilino-4-Amino-6,7-Dimethoxyquinazoline

This compound is prepared by the procedure of Example 34 by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with N-ethylaniline.

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EXAMPLE 45

2-N-Methylbutylamino-4-Amino-6,7-Dimethoxyquinazoline

This compound is prepared by the procedure of Example 34 by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with N-methylbutylamine.

15

15

EXAMPLE 46

2-Amino-4-N-Methylbutylamino-6,7-Dimethoxyquinazoline

This compound is prepared by the procedure of Example 37 by reacting N-methylbutylamine with 2,4-dichloro-6,7-dimethoxyquinazoline, followed by reaction with ethanolic ammonia.

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EXAMPLE 47

The biological activity of the compounds of this invention, particularly in regard to their effectiveness in reducing blood pressure in hypertensive subjects, is illustrated by the following tests on renal hypertensive dogs. The compounds were administered orally in capsule form. The effective dose level was that which lowered the blood pressure from 180/100 to 160/100 mm. Hg. The activity of the compounds is shown in Table XVIII.

25

25

TABLE XVIII

Hypotensive Activity

	Compound	Minimum Effective Concentration mg./kg.
2-chloro-	2-methylamino-4-amino-6,7-dimethoxyquinazoline	2.50
	2-ethylamino-4-amino-6,7-dimethoxyquinazoline	2.50
2-chloro-	2-n-propylamino-4-amino-6,7-dimethoxyquinazoline	2.50
	2-n-butylamino-4-amino-6,7-dimethoxyquinazoline	2.50
	2-isopropylamino-4-amino-6,7-dimethoxyquinazoline	1.25
2-chloro-	2-diethylamino-4-amino-6,7-dimethoxyquinazoline	1.25
	2-[M-methyl-(β -hydroxyethyl)amino]-4-amino-6,7-dimethoxyquinazoline	10
-methyl- on with	2-diallylamino-4-amino-6,7-dimethoxyquinazoline	10
	2-(4-methyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline	2.50
n regard lustrated inistered ie blood s shown	2- β , β , β -trifluoroethylamino-4-amino-6,7-dimethoxyquinazoline	2.50
	2-(4-n-propyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline	2.5
	2-diethanolamino-4-amino-6,7-dimethoxyquinazoline	10
	2-dimethylamino-4-methylamino-6,7-dimethoxyquinazoline	2.50
	2,4-di(diethylamino)-6,7-dimethoxyquinazoline	10
	2,4-di(N,N-dimethylamino)-6,7-dimethoxyquinazoline	10

EXAMPLE 48
Capsules

A blend is prepared containing the following ingredients:

5	Calcium carbonate U.S.P.	17.6	5
	Dicalcium phosphate	18.8	
	Magnesium trisilicate U.S.P.	5.2	
	Lactone U.S.P.	5.2	
	Potato Starch	5.2	
10	Magnesium stearate	1.15	10

To this blend is added sufficient 2-(4-propyl-1-piperazinyl) 4-amino-6,7-dimethoxyquinazoline to provide capsules containing 20, 100 and 250 mg. of active ingredient.

EXAMPLE 49
Injectable Preparation

15	One thousand grams of 2-methylamino-4-amino-6,7-dimethoxyquinazoline are intimately mixed and ground with 2500 grams of sodium ascorbate. The ground dry mixture is filled into vials, sterilized with ethylene oxide and the vials sterilely stoppered. For intravenous administration sufficient water is added to the vials to form a solution containing 10 mg. of active ingredient per milliliter.	15
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EXAMPLE 50
Suspension

A suspension of 2-(N,N-diallylamino)-4-amino-6,7-dimethoxyquinazoline is prepared with the following composition:

Effective ingredient	31.42 g.
70% aqueous sorbitol	714.29 g.
Glycerine U.S.P.	185.35 g.
Gum acacia (10% solution)	100.00 ml.
Polyvinyl pyrrolidone	0.5 g.
Water, distilled to make 1 liter	

To this suspension, various sweetening and flavoring agents may be added by choice. The suspension contains approximately 25 mg. of hypotensive agent per milliliter.

EXAMPLE 51
Solution

A solution of 2-dimethylamino-4-methylamino-6,7-dimethoxyquinazoline is prepared with the following composition.

Effective ingredient	30.22 g.
Magnesium chloride hexahydrate	12.36 g.
Monoethanolamine	8.85 ml.
Propylene glycol	376 g.
Water	94 ml.

The solution has a concentration of 50 mg./ml. and is suitable for parenteral and especially for intramuscular administration.

EXAMPLE 52

The methods employed for the preparation of the compounds of the previous examples are also used to prepare compounds having substituents other than alkoxy on positions 6 and 7 of the quinazoline nucleus. These compounds are prepared from substituted aromatic compounds such as those in Table XIX, followed by chlorination as described in Examples 5, 6, 7 and 8. The substituted aromatic compounds and resulting chlorinated compounds are as follows:

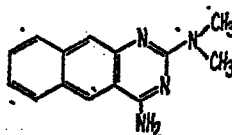
(31)

TABLE XIX

Substituted 2,4-Dichloroquinazolines

Starting Compound	Substituents
4,5-dimethylantranilamide	6,7-dimethyl-
5-pentylantranilic acid	6-pentyl
methyl 4-isopropylantranilate	7-isopropyl-
5-methylantranilic acid	6-methyl-
3-amino-o-tolunitrile	7-methyl-
2-aminopiperonylic acid	6,7-methylenedioxy-
2-amino-4,5-ethylenedioxybenzoic acid	6,7-ethylenedioxy-
2-naphthylamine-3-carboxylic acid	6,7-benzo-
4,5-dimethylantranilic acid	6,7-dimethyl

A specific example of using one of these substituted 2,4-dichloroquinazolines is as follows:



2-Dimethylamino-4-Amino-6,7-Benzoquinazoline

To 8 grams of 2,4-dichloro-6,7-benzoquinazoline, prepared according to the procedure of F. H. S. Curd, et al in the *Journal of the Chemical Society* (London), 1948, p.1761, are added 100 ml. of a 25% solution of anhydrous ammonia in tetrahydrofuran. The reaction mixture is stirred for 44 hours. The precipitate is filtered off and recrystallized from methanol. To the product are added 100 ml. of a 25% solution of dimethylamine in ethanol. The mixture is heated in a sealed pressure bottle for 16 hours at 160°C. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE 53

4-(4-Amino-6,7-dimethoxyquinazoline-2-yl)-Piperazine-1-Carboxylic Acid Isobutyl Ester

Preparation of Isobutyl 1-Piperazinecarboxylate:

To 11.6 grams of anhydrous piperazine in 127 ml. ethanol and 16 ml. water are added with stirring over a 30 minute period, 22.6 grams 48% aqueous hydrobromic acid. The temperature rises to 60°C. during the addition. Isobutyl chloroformate (8.75 grams) is then added over another 30 minute period and the resulting solution is refluxed for 1.5 hours and chilled. The piperazine dihydrobromide which crystallizes is filtered off and the solution is concentrated to an oil *in vacuo*. The oil is taken up in water, neutralized with dilute aqueous sodium hydroxide and extracted with several portions of methylene chloride. The combined extracts are dried with sodium sulfate and the methylene chloride is evaporated to yield 9.9 grams of an oil which is distilled *in vacuo*, b.p. 87—90°C./0.3 mm Hg pressure. The yield of colorless product is 7.17 grams or 60% of theory.

This same procedure is used to prepare 1-(2-furoyl)-piperazine, 1-allylpiperazine, 1-(2-methylallyl)-piperazine, 1-crotonyl-piperazine, propyl-1-piperazine-carboxylate, allyl-1-piperazinecarboxylate, and n-pentyl-1-piperazine-carboxylate.



Preparation of Quinazoline Derivative of Isobutyl 1-Piperazine-carboxylate:

5 A mixture of 7.17 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline and
11.7 grams of isobutyl 1-piperazinecarboxylate in 80 ml. of ethanol is heated in a
pressure bomb at 140°C. for 4 hours. The reaction mixture is cooled and the solvent
evaporated. The resulting residue is triturated with 300 ml. water. The insoluble
material is filtered from the water and dissolved in 50 ml. methanol. The methanol
is displaced with 50 ml. of ethyl acetate and the product is precipitated and collected
by filtration. The product is dissolved in warm ethanol-1N hydrochloric acid and
10 chilled. The crystals of the resulting hydrochloride are filtered from the solvent and
dried to yield 8.1 grams of product (62% of theory) melting at 277—278°C. 10

Anal. Calcd. for $C_{19}H_{27}O_4N_5$ HCl $1/2 H_2O$:

C, 52.47; H, 6.72; N, 16.12; Cl, 8.15.

Found: C, 52.69; H, 6.86; N, 16.23; Cl, 7.86.

EXAMPLE 54

15 2-(4-Allyl-1-piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline
To 18.9 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline in 280 ml. of
isoamyl alcohol are added 19.9 grams of 1-allylpiperazine prepared as in Example 53. 15
The mixture is refluxed for 20 hours, and cooled. The 1-allylpiperazine hydrochloride
formed is extracted with water and the organic layer is concentrated *in vacuo* to an
oil which crystallizes when triturated with hexane. The solids are collected by filtration
20 and dried to give 20.4 grams of product, m.p. 198—201°C. 20

The hydrochloride salt is prepared by redissolving the product in ethanol/1N
hydrochloric acid and chilling. The resulting crystals, when dried melt at 282—283°C.

EXAMPLE 55

25 2-(4-Benzylpiperidino)-4-Amino-6,7-Dimethoxyquinazoline
To 7.17 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline in ethanol are added
10.5 grams 4-benzylpiperidine. The mixture is heated in a pressure bottle for 4 hours
at 140°C. The mixture is cooled, the solvent is evaporated and the residue is
redissolved in methanol-chloroform (1:1). This solvent is displaced with ethyl acetate
causing crystallization of product. The crystals collected weigh 6.8 grams, m.p.
30 260—262°C. 30

Anal. Calcd. for $C_{22}H_{26}O_2N_4$ HCl: C, 63.68; H, 6.56; N, 13.50;

Cl, 8.55.

Found: C, 63.76; H, 6.58; N, 13.72;

Cl, 8.43

EXAMPLE 56

4-(4-Amino-6,7-dimethoxyquinazoline-2-yl)-Piperazine-1-Carboxylic Acid
Ethyl Ester Hydrochloride

35 This compound is prepared from ethyl 1-piperazine-carboxylate and 2-chloro-4-
amino-6,7-dimethoxy quinazoline according to the procedure of Example 53. 35

Anal. Calcd. for $C_{17}H_{23}O_4N_5$ HCl $1/2 H_2O$:

C, 50.19; H, 6.19; N, 17.22; Cl, 8.71

Found: C, 49.78; H, 6.15; N, 17.11; Cl, 8.70

M.p. 277—278°C.

(29)

EXAMPLE 57

4-(4-Amino-6,7-dimethoxyquinazoline-2-yl)-Piperazine-1-Carboxylic Acid
Allyl Ester Hydrochloride

This compound is prepared from allyl 1-piperazine-carboxylate and 2-chloro-4-amino-6,7-dimethoxyquinazoline according to the procedure of Example 53. The hydrochloride melts at 260—262°C.

EXAMPLE 58

2-[4-(β -Hydroxyethyl)-piperidino]-4-Amino-6,7-Dimethoxyquinazoline
Hydrochloride

This compound is prepared according to the procedure of Example 27 from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 1- β -hydroxyethylpiperidine. The hydrochloride salt is prepared according to the procedure of Example 24. The compound melts at 239—240°C.

Anal. Calcd. for $C_{17}H_{24}O_3N_4$ HCl $1/2$ H_2O :

C, 54.04; H, 6.93; N, 14.83; Cl, 9.38.

Found: C, 54.36; H, 7.11; N, 14.95; Cl, 9.22.

EXAMPLE 59

2-(4-n-Propylpiperidino)-4-Amino-6,7-Dimethoxyquinazoline Hydrochloride

This compound is prepared from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 4-n-propylpiperidine according to the procedures of Examples 27 and 24. The free base melts at 150—151°C. The hydrochloride melts at 246—247°C.

Anal. Calcd. for $C_{18}H_{26}O_2N_4$: C, 65.43; H, 7.92; N, 16.95.

Found: C, 65.23; H, 7.90; N, 16.84.

Anal. Calcd. for $C_{18}H_{26}O_2N_4$ HCl $1/2$ H_2O :

C, 57.51; H, 7.51; N, 14.91;

Cl, 9.43.

Found: C, 57.70; H, 7.59; N, 14.94;

Cl, 9.70

EXAMPLE 60

2-(4-n-Heptanoyl-1-piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline
Hydrochloride

This compound is prepared from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 1-n-heptanoylpiperazine according to the procedures of Examples 27 and 24. The product melts at 155—162°C.

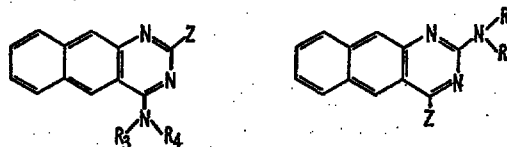
Anal. Calcd. for $C_{21}H_{31}O_3N_5$ HCl $1/2$ H_2O :

C, 56.44; H, 7.44; N, 15.67; Cl, 7.93.

Found: C, 56.31; H, 7.62; N, 15.34; Cl, 7.34.

EXAMPLE 61

The 2,4-disubstituted-6,7-benzoquinazolines of the formulae:



5 are prepared from 2,4-dichloro-6,7-benzoquinazoline, as described in Example 52, and by the procedures of Examples 20, 27 and 28. These compounds are listed in Table XX.

TABLE XX

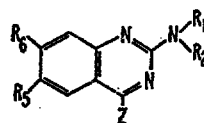
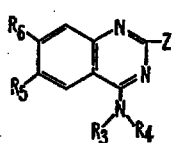
R ₁ or R ₃	R ₂ or R ₄	Z
H—	H—	piperidino
H—	H—	morpholino
H—	H—	4-methyl-1-piperidino
H—	H—	4-pentyl-1-piperidino
CH ₂ =CH—CH ₂ —	H—	3-oxo-piperaziny1
CH ₂ =CH—CH ₂ —	H—	4-acetyl-1-piperaziny1
CH ₂ =CH—CH ₂ —	H—	4-benzoyl-1-piperaziny1
CH ₂ =CH—CH ₂ —	H—	4-carbamoyl-1-piperaziny1
C ₆ H ₅ —	C ₆ H ₅ —	4-ethylcarbamoyl-1-piperaziny1-
C ₆ H ₅ —	C ₆ H ₅ —	4-methylcarbamoyl-1-piperaziny1-
C ₆ H ₅ —	C ₆ H ₅ —	4-diethylcarbamoyl-1-piperaziny1-
C ₆ H ₅ —	C ₆ H ₅ —	4-n-propylcarbamoyl-1-piperaziny1-
C ₆ H ₅ —	C ₆ H ₅ —CH ₂ —	4-dimethylcarbamoyl-1-piperaziny1-
C ₆ H ₅ —CH ₂ —	H—	2-hydroxypiperidino
C ₆ H ₅ —CH ₂ —	C ₆ H ₅ —CH ₂ —	4-hydroxypiperidino
HO—CH ₂ —	H—	2-methoxypiperidino
4—Cl—C ₆ H ₄ —	H—	2-butoxypiperidino
4—Cl—C ₆ H ₄ —	H—	4-butoxypiperidino
3—Br—C ₆ H ₄ —	C ₆ H ₅ —	2-methylpiperidino
2—OH—C ₆ H ₄ —	H—	4-methylpiperidino
2—OH—C ₆ H ₄ —	H—	cyclopropylamino
C ₆ H ₅ —	C ₆ H ₅ —	cyclobutylamino

TABLE XX—continued

R_1 or R_3	R_2 or R_4	Z
$\text{CH}_2=\text{CH}-\text{CH}_2-$	$\text{CH}_2=\text{CH}-\text{CH}_2-$	cycloheptylamino
$\text{HO}-\text{CH}_2-$	$\text{HO}-\text{CH}_2-$	2-hexylpiperidino
$\text{HO}-(\text{CH}_2)_5-$	H—	2-benzylpiperidino
$2-\text{CH}_3\text{O}-\text{C}_6\text{H}_4-$	H—	2-hydroxymethylpiperidino
$3-\text{CH}_3\text{O}-\text{C}_6\text{H}_4-$	H—	4-hydroxymethylpiperidino
$2-\text{C}(\text{F})_3-\text{CH}_2-$	H—	4-acetyl-1-piperazinyl
$2-\text{C}(\text{F})_3-\text{CH}_2-$	H—	4-caproyl-1-piperazinyl
$2-\text{C}_6\text{H}_{13}-\text{C}_6\text{H}_4-$	H—	4-(2-furoyl)-1-piperazinyl
$3-\text{F}-\text{C}_6\text{H}_4-$	H—	4-(3-thenoyl)-1-piperizinyl-
$4-\text{F}-\text{C}_6\text{H}_4-$	H—	4-(2-methylphenyl)-1-piperazinyl
C_6H_5-	C_6H_5-	4-(2-trifluoromethylbenzoyl)-1-piperazinyl

EXAMPLE 62

The 2,4-disubstituted 6(7)-methoxyquinazolines of the formulae:



are prepared by the procedures of Example 20. These compounds are listed in Table XXI.

TABLE XXI

R_1 or R_3	R_2 or R_4	R_5	R_6	Z
H—	H—	H—	$\text{CH}_3\text{O—}$	2-hydroxypiperidino
H—	H—	H—	$\text{CH}_3\text{O—}$	4-hydroxypiperidino
H—	H—	H—	$\text{CH}_3\text{O—}$	2-methoxypiperidino
$\text{CH}_2=\text{CH—CH}_2\text{—}$	H—	H—	$\text{CH}_3\text{O—}$	4-methoxypiperidino
$\text{CH}_2=\text{CH—CH}_2\text{—}$	H—	$\text{C}_2\text{H}_5\text{O}$	$\text{CH}_3\text{O—}$	2-butoxypiperidino
$\text{CH}_2=\text{CH—CH}_2\text{—}$	C_2H_5	CH_3O	$\text{CH}_3\text{O—}$	cyclopropylamino
$\text{C}_6\text{H}_5\text{—}$	H—	$\text{C}_2\text{H}_5\text{O—}$	$\text{CH}_3\text{O—}$	4-butoxypiperidino
$\text{C}_6\text{H}_5\text{—}$	$\text{C}_6\text{H}_5\text{—}$	$\text{CH}_3\text{O—}$	H—	2-methylpiperidino
$\text{C}_6\text{H}_5\text{—CH}_2\text{—}$	$\text{C}_6\text{H}_5\text{—}$	$\text{CH}_3\text{O—}$	H—	4-methylpiperidino
$\text{C}_6\text{H}_5\text{—CH}_2\text{—}$	$\text{CH}_2=\text{CH—CH}_2$	$\text{CH}_3\text{O—}$	H—	2-hexylpiperidino
$\text{CH}_2=\text{CH—CH}_2\text{—}$	H—	$\text{CH}_3\text{O—}$	$\text{CH}_3\text{O—}$	2-benzylpiperidino
$\text{C}_6\text{H}_5\text{—CH}_2\text{—}$	H—	$\text{CH}_3\text{O—}$	$\text{CH}_3\text{O—}$	4-benzylpiperidino
$\text{C}_6\text{H}_5\text{—CH}_2\text{—}$	$\text{C}_6\text{H}_5\text{—CH}_2\text{—}$	$\text{CH}_3\text{O—}$	$\text{CH}_2\text{O—}$	2-hydroxymethylpiperidino
$\text{C}_6\text{H}_5\text{—}$	$\text{C}_6\text{H}_5\text{—}$	$\text{CH}_3\text{O—}$	H—	4-hydroxymethylpiperidino
2—Cl— C_6H_4	H—	$\text{CH}_3\text{O—}$	$\text{CH}_3\text{O—}$	4-(6-hydroxyhexyl)-piperidino
3—Cl— $\text{C}_6\text{H}_4\text{—}$	H—	$\text{CH}_3\text{O—}$	$\text{CH}_3\text{O—}$	4-(4-hydroxyhexyl)-piperidino

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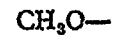


TABLE XXI—continued

R ₁ or R ₃	R ₂ or R ₄	R ₅	R ₆	Z
2,4-Cl ₂ C ₆ H ₃ -	H-	CH ₃ O-	CH ₃ O-	4-acetyl-1-piperazinyl
3-HO-C ₆ H ₄ -	H-	CH ₃ O-	H-	4-caproyl-1-piperazinyl
4-HO-C ₆ H ₄ -	H-	CH ₃ O-	H-	4-heptanoyl-1-piperazinyl
HO-CH ₂ -	H-	CH ₃ O-	H-	4-(2-furoyl)-1-piperazinyl
HO-CH ₂ -	HO-CH ₂	CH ₃ O-	H-	4-(3-furoyl)-1-piperazinyl
2-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(2-thenoyl)-1-piperazinyl
3-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(3-thenoyl)-1-piperazinyl
4-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(2-methylallyl)-1-piperazinyl
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	CH ₃ O-	H-	4-(2-methoxyphenyl)-1-piperazinyl
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	CH ₃ O-	H-	4-(3-methoxyphenyl)-1-piperazinyl
C ₆ H ₅ -	C ₆ H ₅ -	H-	CH ₃ O-	4-(4-methoxyphenyl)-1-piperazinyl
C ₆ H ₅ -	C ₆ H ₅ -	H-	CH ₃ O-	4-(2-trifluoromethylphenyl)-1-piperazinyl
CH ₃ =CH-CH ₂ -	CH ₃ -	CH ₃ O-	CH ₃ O-	4-crotonyl-1-piperazinyl
C ₆ H ₅ -CH ₂ -	H-	CH ₃ O-	CH ₃ O-	4-(3-trifluoromethylphenyl)-1-piperazinyl
C ₆ H ₅ -CH ₂ -	H-	CH ₃ O-	CH ₃ O-	4-(4-trifluoromethylphenyl)-1-piperazinyl
2-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(2-methylphenyl)-1-piperazinyl

TABLE XXI—continued

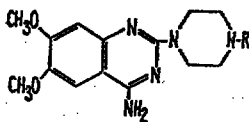
R_1 or R_3	R_2 or R_4	R_5	R_6	Z
3-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(3-methylphenyl)-1-piperazinyI
4-CH ₃ -C ₆ H ₄ -	H-	CH ₃ O-	CH ₃ O-	4-(4-methylphenyl)-1-piperazinyI
C ₆ H ₅ -	H-	CH ₃ O-	CH ₃ O-	4-(2-methylbenzoyl)-1-piperazinyI
C ₆ H ₅ -	H-	CH ₃ O-	CH ₃ O-	4-(3-methylbenzoyl)-1-piperazinyI
C ₆ H ₅ -	H-	C ₆ H ₅ O-	CH ₃ O-	4-(4-methylbenzoyl)-1-piperazinyI
C ₆ H ₅ -	H-	C ₂ H ₅ O-	CH ₃ O-	4-(2-trifluoromethylbenzoyl)-1-piperazinyI
C ₆ H ₅ -	C ₆ H ₅ -	C ₂ H ₅ O-	CH ₃ O-	4-(3-trifluoromethylbenzoyl)-1-piperazinyI
C ₆ H ₅ -	C ₆ H ₅ -	CH ₃ O-	H-	4-(4-trifluoromethylbenzoyl)-1-piperazinyI
CH ₂ =CH-CH ₂ -	H-	CH ₃ O-	H-	4-(2-methoxybenzoyl)-1-piperazinyI
CH ₂ =CH-CH ₂ -	H-	CH ₃ O-	H-	4-(3-methoxybenzoyl)-1-piperazinyI
CH ₂ =CH-CH ₂ -	H-	CH ₃ O-	H-	4-(4-methoxybenzoyl)-1-piperazinyI
C ₆ H ₅ -	H-	CH ₃ O-	CH ₃ O-	4-carbamoyl-1-piperazinyI
C ₆ H ₅ -	H-	CH ₃ O-	CH ₃ O-	4-methylcarbamoyl-1-piperazinyI
C ₆ H ₅ -CH ₂ -	H-	CH ₃ O-	CH ₃ O-	4-ethylcarbamoyl-1-piperazinyI
C ₆ H ₅ -CH ₂ -	C ₆ H ₅ -CH ₂ -	CH ₃ O-	CH ₃ O-	4-n-propylcarbamoyl-1-piperazinyI
C ₆ H ₅ -CH ₂ -	H-	CH ₃ O-	CH ₃ O-	4-diethylcarbamoyl-1-piperazinyI
C ₆ H ₅ -	H-	CH ₃ O-	CH ₃ O-	4-di-n-propylcarbamoyl-1-piperazinyI
C ₆ H ₅ -	C ₆ H ₅ -	CH ₃ O-	CH ₃ O-	4-dimethylpropylcarbamoyl-1-piperazinyI

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EXAMPLE 63

The biological activity of the compounds of this invention was tested according to the procedure of Example 47. The activity of the compounds is given in Table XVIII of Example 47 and Table XXII.

TABLE XXII
Hypotensive Activity



R	Minimum Effective Concentration mg./kg.
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2=\text{C}-\text{CH}_2- \end{array}$	1.25
$\begin{array}{c} \text{O} \\ \\ \text{C}_2\text{H}_5\text{O}-\text{C}- \end{array}$	0.075
$\begin{array}{c} \text{O} \\ \\ \text{CH}_2=\text{CH}-\text{CH}_2-\text{O}-\text{C}- \end{array}$	1.25
$\begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2-\text{O}-\text{C}- \\ \\ \text{CH}_3 \end{array}$	0.075
2-(4-hydroxy-1-piperidino)-4-amino-6,7-dimethoxyquinazoline	1.25

EXAMPLE 64

2-Diethylamino-4-Chloro-6,7-Dimethoxyquinazoline

A mixture of 10 grams 2-diethylamino-6,7-dimethoxy-4(3H)-quinazolinone hydrochloride in 50 ml. of phosphorous oxychloride is refluxed for 2 hours. The liquids are evaporated to give a crystalline residue of 2-diethylamino-4-chloro-6,7-dimethoxyquinazoline hydrochloride, m.p. 175—184°C. The product is dissolved in dilute sodium hydrogen carbonate aqueous solution and is extracted several times with chloroform. The combined chloroform extracts are dried with sodium sulfate and the solvent is evaporated to yield 7.6 grams (82% of theory) of product, m.p. 129—131°C.

Anal. Calcd. for $C_{14}H_{18}O_2N_8$ Cl: C, 56.86; H, 6.13; N, 14.21.

Found: C, 56.81; H, 6.08; N, 13.97.

EXAMPLE 65

2-Diethylamino-4-Amino-6,7-Dimethoxyquinazoline

The product of Example 64 is dissolved in 100 ml. tetrahydrofuran and a solution of anhydrous ammonia in tetrahydrofuran is added. The mixture is stirred at room temperature for 24 hours and the resulting precipitate is collected. The product is recrystallized from isopropyl alcohol. The dried product melts at 179—180°C.

EXAMPLE 66

2-(4-Allyl-1-piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline

To 10 grams of 6,7-dimethoxy-(1H, 3H)-quinazolinedione in 200 ml. pyridine are added 30 grams phosphorous pentasulfide and the mixture is refluxed with continuous stirring for 5 hours. The solvent is removed under reduced pressure and the residue is decomposed with hot water. The solid material is filtered from the mixture. The product is 6,7-dimethoxy-(1H,3H)-quinazolinedithione.

To 0.1 mole of 6,7-dimethoxy-(1H,3H)-quinazolinedithione in 220 ml. 1N potassium hydroxide solution and 100 ml. methanol, is added slowly with stirring, 0.22 mole of methyl iodide. The mixture is heated on a steam bath for 2 hours, cooled, and the resulting precipitate is filtered from the mixture. The product is 2,4-di-methylmercapto-6,7-dimethoxyquinazoline.

To 0.1 mole of 2,4-dimethylmercapto-6,7-dimethoxyquinazoline in 200 ml. of tetrahydrofuran is added a solution of 0.1 mole of anhydrous ammonia in tetrahydrofuran. The mixture is stirred at room temperature for 18 hours and the precipitate which forms is collected and recrystallized from dimethylformamide/water to yield 2-methylmercapto-4-amino-6,7-dimethoxyquinazoline.

A mixture of 0.1 mole of 2-methylmercapto-4-amino-6,7-dimethoxyquinazoline and 0.12 mole of 1-allylpiperazine in isoamyl alcohol is heated at reflux for 13 hours. The reaction mixture is cooled, washed with water, and the organic layer is concentrated *in vacuo*. Hexane is slowly added to the oily residue and the solids which form are collected. The product is 2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline, m.p. 198—201°C.

EXAMPLE 67

2-(4-Allyl-1-piperazinyl)-4-Amino-6,7-Dimethoxyquinazoline

To 0.10 mole of 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline in 300 ml. of methanol at 50°C. is added with vigorous stirring 0.10 mole allyl bromide. The mixture is heated at reflux for 2 hours, cooled, and the crystalline material is filtered. Recrystallization from ethanol yields the desired product.

EXAMPLE 68

2-[4-(2-Furoyl)-piperazine-1-yl]-4-Amino-6,7-Dimethoxyquinazoline

To 0.10 mole 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline in 300 ml. methanol is added with vigorous stirring, 0.10 mole 2-furoyl chloride. After addition is complete, the mixture is stirred for 3 hours at room temperature. The solids are filtered to give the desired product, m.p. 278—280°C.

EXAMPLE 69

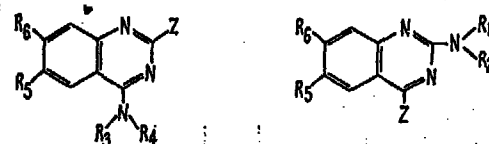
2-Diethylamino-4-Amino-6,7-Dimethoxyquinazoline

To 0.1 mole 2-amino-4,5-dimethoxybenzonitrile in dimethylformamide is added 0.5 mole of N,N-diethylguanidine. The mixture is heated for 12 hours at 150°C. The solution is concentrated to a small volume, *in vacuo*. Water is added and the mixture is chilled. The solids which crystallize are filtered from the mixture and recrystallized from iso-propyl alcohol to give the desired product.

pyridine-
con-
and the
mixture.
ml. 1N
stirring,
cooled,
methyl-
0 ml. of
hydroxy-
acetate
to yield
13 hours.
concent-
h form
pyridine-
300 ml.
The
filtered.
300 ml.
addition
solids are
is added
150°C.
and the
mixture and

EXAMPLE 70

The 2,4-disubstituted-6,7-alkylquinazolines of the formula:



where R₁, R₂, R₃, R₄, R₅, R₆ and Z are as indicated in Table XXIII, are prepared by the procedures of Examples 13, 14, 17, 19, 20, 26 and 33. These compounds are listed in Table XXIII.

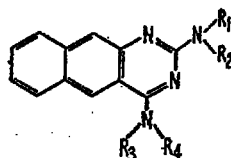
TABLE XXIII

R ₁ or R ₃	R ₂ or R ₄	R ₅	R ₆	Z
H—	H—	H—	CH ₃ —	cyclopropylamino—
H—	H—	CH ₃ —	CH ₃ —	4-crotonyl-1-piperazinyl—
H—	H—	CH ₃ —	H—	3-hydroxypiperidino—
H—	CH ₃ —	C ₂ H ₅ —	H—	3-methoxypiperidino—
H—	C ₂ H ₅ —	H—	C ₂ H ₅ —	3-n-propoxypiperidino—
H—	n-C ₃ H ₇ —	n-C ₃ H ₇ —	CH ₃ —	3-n-butoxypiperidino—
H—	H—	n-C ₃ H ₇ —	n-C ₃ H ₇ —	3-hydroxymethylpiperidino—
CH ₃ —	H—	iso-C ₃ H ₇ —	iso-C ₃ H ₇ —	3-hydroxyhexylpiperidino—
CH ₃ —	CH ₃ —	C ₂ H ₅ —	C ₂ H ₅ —	cyclopropylamino—
n-C ₃ H ₇ —	n-C ₃ H ₇ —	CH ₃ —	H—	piperidino—
CH ₃ C—CH ₂ —	CH ₃ —	CH ₃ —	CH ₃ —	piperidino—
CH ₂ =CH—CH ₂ —	CH ₂ =CH—CH ₂ —	CH ₃ —	CH ₃ —	4-(3-furoyl)-1-piperazinyl—
CH ₂ =CH—CH ₂ —	CH ₂ =CH—CH ₂ —	CH ₃ —	CH ₃ —	4-crotonyl-1-piperazinyl—

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EXAMPLE 71

The 2,4-disubstituted-6,7-benzoquinazolines of the formula:



are prepared from 2,4-dichloro-6,7-benzoquinazoline, as described in Example 54 and by the procedures of Examples 17, 20, 27, 28 and 23. These compounds are listed in Table XXIV.

TABLE XXIV

R ₁	R ₂	R ₃	R ₄
H—	H—	H—	H—
CH ₃ —	H—	H—	H—
CH ₃ —	CH ₃ —	CN ₃ —	H—
CH ₃ —	H—	CH ₃ —	CH ₃ —
C ₂ H ₅ —	H—	C ₂ H ₅ —	CH ₃ —
n—C ₃ H ₇ —	H—	n—C ₃ H ₇ —	H—
n—C ₃ H ₇ —	n—C ₃ H ₇ —	n—C ₃ H ₇ —	n—C ₃ H ₇ —
iso—C ₃ H ₇ —	iso—C ₃ H ₇ —	H—	H—
CH ₂ =CH—CH ₂ —	H—	CH ₂ =CH—CH ₂ —	H—
CH≡C—CH ₂ —	H—	CH ₃ —	H—
CH≡C—CH ₂ —	CH ₃ —	H—	H—
CH≡C—CH ₂ —	C ₂ H ₅ —	H—	H—
C ₆ H ₅ —	H—	CH≡C—CH ₂ —	H—
C ₆ H ₅ —CH ₂ —	H—	C ₆ H ₅ —	H—
HO—CH ₂ —	H—	HO—CH ₂ —	H—
4—Cl—C ₆ H ₄ —	H—	C ₆ H ₅ —	H—
3—Br—C ₆ H ₄ —	H—	4—Cl—C ₆ H ₄ —	H—

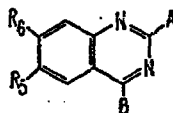
WHAT WE CLAIM IS:—

1. A quinazoline of formula I, II, or III herein with the proviso that in a quinazoline of formula I herein, when R₅ and R₆ are both methoxy and R₃ and R₄ are both hydrogen, then R₁ and R₂ may not both be methyl or hydrogen.
2. 2-(4-Allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline.
3. 2-(4-Methyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline.
4. 2-(4-n-Propyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline.
5. 2-(4-Benzoyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline.
6. 2-[4-(2-Furoyl)-1-piperazinyl]-4-amino-6,7-dimethoxyquinazoline.
7. 4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-carboxylic acid isobutyl ester.

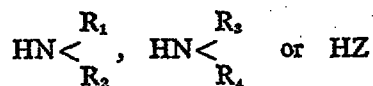
8. A pharmaceutical composition comprising a quinazoline compound according to claim 1 and a pharmaceutically acceptable carrier.

9. A process for preparing a quinazoline compound according to claim 1 which comprises

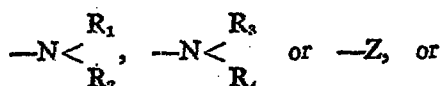
(a) reacting a quinazoline of the formula



with the appropriate quantity of an amine of the formula:



wherein A and/or B are halogen, mercapto, ether or thioether groups or one of them is

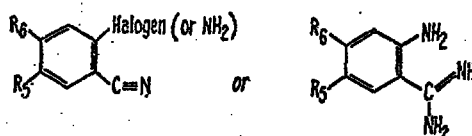


(b) and when required, then alkylating, aralkylating or alkenylating the product of step (a) to replace a hydrogen atom on a nitrogen atom of R₁ to R₄ and Z and/or alkanoylating or aroylating Z.

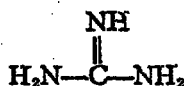
(c) and further, when required, forming the pharmaceutically acceptable acid addition salt.

10. A process for producing a quinazoline compound according to claim 1 which comprises

(a) reacting a compound of the formula



with a guanidine of the formula



(b) and when required, forming the pharmaceutically acceptable acid addition salt.

11. A process for preparing quinazoline compounds of formulas I, II and III substantially as described.

12. Compounds according to claim 1 whenever prepared by the process substantially as described.

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