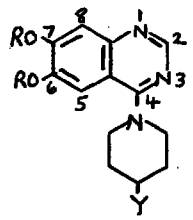
SPECIFICATION

6,7-Dialkoxy-4-(4-substituted-piperidino)-quinazolines

This invention relates to therapeutic agents, which are novel derivatives of quinazoline, and is particularly concerned with such derivatives having a substituted piperidino group in the 4-position.

The compounds of the invention are phosphodiesterase inhibitors and cardiac stimulants of which a preferred class selectively increase the force of myocardial contraction without producing significant increases in heart rate. The compounds are useful in the curative or prophylactic treatment of cardiac conditions, particularly heart failure.

According to the invention there is provided novel quinazoline compounds of the formula:



(I)

wherein R is a lower alkyl group;

and Y represents a group of the formula:

$$—CHR^1)_m—Z$$

wherein R^1 is a hydrogen atom or a lower alkyl group, and m is 1 or 2, with the proviso that when m is 2, each R^1 may be the same or different;

and

Z is a group selected from:

—$OCONR^4R^5$

—$N(R^2)COR^3$

—$N(R^2)SO_2R^3$

and —$N(R^2)CONR^4R^5$

wherein R^2 is hydrogen or lower alkyl, R^3 is lower alkyl, benzyl, or phenyl, and R^4 and R^5 are each independently hydrogen or a group as defined for R^3 above; and the pharmaceutically acceptable acid addition salts thereof.

The term "lower" applied to an alkyl or alkoxy group indicates that such a group contains up to 6 carbon atoms, preferably up to 4 carbon atoms, and such groups may be straight or, when appropriate, branched chain.

The compounds of the invention containing one or more asymmetric centres will exist as one or more pairs of enantiomers, and such pairs of individual isomers may be separable by physical methods, e.g. by fractional crystallisation of suitable salts. The invention includes the separated pairs as well as mixtures thereof, as racemic mixtures or as separated d- and 1- optically-active isomeric forms.

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

The cardiac stimulant activity of the compounds of the invention is shown by their effectiveness in one or more of the following tests (a) increasing the force of contraction in the isolated, spontaneously beating, guinea pig double atria preparation; (b) increasing myocardial contractility (left ventricular $dP/_{dt}$ max.) in the anaesthetised dog with a left ventricular catheter; (c) increasing myocardial contractility in the conscious dog with an implanted left ventricular transducer.

In test (a) the positive inotropic and chronotropic responses of the atria to the test compound are measured at several doses and compared with the responses elicited by isoprenaline. The comparison of the dose response curves obtained gives a measure of the force versus rate selectivity of the test compound.

In test (b) the positive inotropic action of the test compound following intravenous administration is measured in the anaesthetised dog. The magnitude and duration of the inotropic action and the selectivity for increase in force versus frequency of contraction of the test compound are obtained, as are its peripheral effects, e.g. the effect on the blood pressure.

In test (c) the positive inotropic action of the test compound following intravenous or oral administration to a conscious dog with an implanted left ventricular transducer is measured. The magnitude and duration of this action and the selectivity for increase in force versus frequency of contraction of the test compound are all obtained.

As a result of the above tests, the following have been found to be preferred:—

R is preferably methyl.

"$—(CHR^1)_m—$" is preferably $—CH_2—$, $—CH_2CH_2—$, or $—CH(CH_3)CH_2—$.

Z is preferably:

(a) $—OCONHR^5$ wherein R^5 is a $C_1—C_4$ alkyl group;

(b) $—N(R^2)COR^3$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^3 is a $C_1—C_4$ alkyl group;

(c) $—N(R^2)SO_2R^3$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^3 is $C_1—C_4$ alkyl, phenyl or benzyl; or

(d) $—N(R^2)CONHR^5$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^5 is a $C_1—C_4$ alkyl group.

The most preferred individual compounds are those of the formula (I) in which R is CH_3 and Y is either;

$—CH_2CH_2OCONHC_2H_5$,

$—CH_2CH_2NHSO_2CH_3$,

$—CH_2CH_2N(CH_3)SO_2CH_3$,

$—CH_2N(CH_3)CONH(CH_2)_2CH_3$,

$—CH_2CH_2N(CH[CH_3]_2)SO_2CH_3$,

$—CH(CH_3)CH_2N(CH_3)SO_2CH_3$,

$—CH(CH_3)CH_2N(CH_3)COCH_3$,

$—CH_2N(CH_3)CONH(CH_2)_3CH_3$,

$—CH(CH_3)CH_2N(CH_3)SO_2C_2H_5$,

The compounds of the invention can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

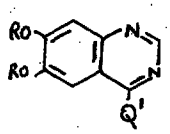
For administration to man in the curative or prophylactic treatment of cardiac conditions such as congestive heart failure, it is expected that oral dosages of the most active compounds of the invention will be in the range from 20 mg to 1 g daily, taken in 2 to 4 divided doses per day, for an average adult patient (70 kg). Dosages for intravenous administration would be expected to be within the range 1 to 300 mg per single dose as required, for example in the treatment of acute heart failure. Thus for a typical adult patient, individual tablets or capsules might contain from 5 to 250 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier.

Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above or pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier.

The compounds of the invention may be prepared by a number of routes:

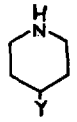
Route A

Compounds of the formula (I) may be prepared by reacting an appropriately substituted quinazoline of the formula:



(II)

wherein Q^1 represents a facile leaving group such as chloro-, bromo-, iodo-, lower alkoxy or (lower alkyl) thio, with an amine of the formula:



(III)

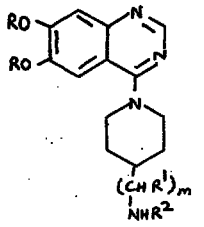
with resultant elimination of HQ^1. Q^1 is preferably chloro or bromo. The reaction is preferably carried out in an inert organic solvent such as ethanol with heating, e.g. under reflux, in a temperature range of 75° to 150°C for up to about 4 hours. When Q^1 is chloro-, bromo- or iodo-, the presence of a base such as triethylamine or of excess reagent of the formula (III) is advantageous.

The product may be isolated and purified by conventional methods.

The compounds of the formula (III) are either known compounds or may be prepared by procedures analogous to the prior art, e.g. by the hydrogenation of the corresponding pyridine derivatives which may themselves be prepared by conventional methods.

Route B

Compounds of the formula (I) in which Z is —N(R^2CONHR^5 may be prepared by the reaction of a quinazoline of the formula:



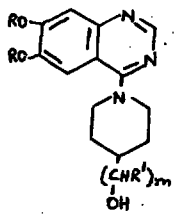
(IV)

with an isocyanate R^5NCO, R^5 being other than hydrogen, or, to prepare compounds in which R^5 is H, sodium or potassium cyanate in the presence of acid. The acid may be supplied by using an acid-addition salt of the compound of the formula (IV) as the starting material. The reaction is typically carried out by stirring the reactants together in an inert organic solvent, e.g. chloroform, at room temperature for up to about 72 hours. The product may be isolated and purified by conventional procedures.

The starting materials of the formula (IV) may be prepared by conventional procedures.

Route C

Compounds of the formula (I) wherein Z is —OCONHR^5 may be prepared by reacting a quinazoline of the formula:



(V)

with an isocyanate R^5NCO, R^5 being other than hydrogen, or, to prepare compounds in which R^5 is hydrogen, sodium or potassium cyanate in the presence of acid. The reaction is typically carried out by stirring the reactants together in an inert organic solvent, e.g. chloroform, at room temperature for up to 24 hours, although some heating may be necessary.

The starting materials of the formula (V) may be prepared by conventional procedures.

The final product may be isolated and purified by conventional methods.

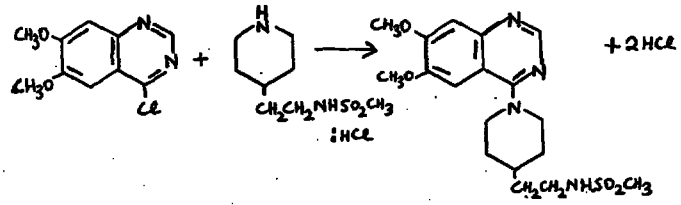
Acid addition salts of the compounds of formula (I) may be prepared from the crude or pure free base product by the conventional technique of reacting the free base with the acid in an inert solvent, e.g. by mixing alcoholic solutions of each and collecting the resulting precipitate by filtration. The product may then be recrystallised to purity.

The quinazoline starting materials used in the preceding routes may be prepared by procedures analogous to those of the prior art. Similarly the piperidine and other starting materials used are either known compounds or may be prepared by conventional methods.

The following Examples illustrate the invention:

EXAMPLE 1

Preparation of 6,7-dimethoxy-4-[4-(2-methanesulphonamidoethyl)piperidino]quinazoline



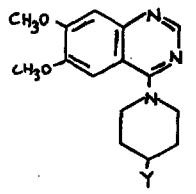
4-Chloro-6,7-dimethoxy quinazoline (1.1 g), 4-(2-methanesulphonamidoethyl)piperidine hydrochloride (1.5 g) and triethylamine (1.5 ml) in ethanol (30 ml) were heated together under reflux for 1½ hours. The solution was then cooled to room temperature, concentrated *in vacuo*, suspended in water (70 ml) and basified to pH 10 with 10% aqueous sodium carbonate solution. The mixture was extracted with chloroform (2 x 70 ml), the extracts combined, dried ($MgSO_4$), and taken to dryness *in vacuo*. The resultant pale yellow oil was triturated with ether (70 ml) to give a white solid which was collected by filtration. Crystallisation of this solid from ethanol yielded 6,7-dimethoxy-4-[4-(2-methanesulphonamidoethyl)piperidino]quinazoline (1.7 g), m.p. 162—164°C.

Analysis %:—

Found: C, 54.8; H, 6.6; N, 14.4

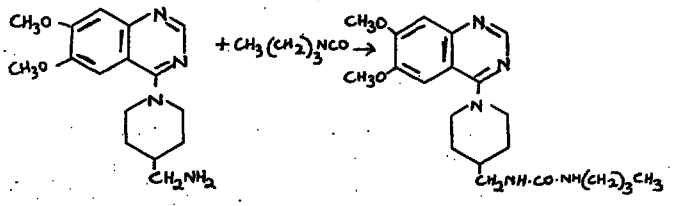
Calculated for $C_{18}H_{28}N_4O_4S$: C, 54.8; H, 6.6; N, 14.2.

The following compounds were prepared similarly to Example 1, starting from 4-chloro-6,7-dimethoxyquinazoline and the appropriate 4-substituted piperidine:



Example No.	Y	Form isolated and m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
2	$-CH_2CH_2NHCONHC_2H_5$	Free base, 198 – 201°	61.7 (62.0	7.6 7.5	18.2 18.1)
3	$-CH_2NHCOCH_3$	Free base, 177 – 181°	62.4 (62.8	6.9 7.0	16.2 16.3)
4	$-CH_2CH_2N(CH_3)SO_2CH_3$	Free base, 175°	55.4 (55.9	7.0 6.9	13.9 13.7)
5	$-CH_2CH_2N(CH_3)CONHC_2H_5$	Free base, 170 – 171°	62.1 (62.8	7.7 7.8	17.3 17.4)
6	$-CH_2N(CH_3)CONH(CH_2)_2CH_3$	Free base, 163 – 165°	62.6 62.8	7.8 7.8	17.2 17.4)
7	$-CH_2CH_2NHSO_2$.Phenyl	Free base, 178 – 180°	60.2 (60.5	6.1 6.2	11.7 12.3)
8	$-CH_2CH_2N(CH[CH_3]_2)SO_2CH_3$	Hydrochloride, 221 – 224°	53.0 (53.3	7.1 7.0	11.8 11.8)
9	$-CH(CH_3)CH_2N(CH_3)SO_2CH_3$	Hydrochloride monohydrate, 183 – 188°	50.5 (50.4	7.0 7.0	11.7 11.7)
10	$-CH(CH_3)CH_2N(CH_3)COCH_3$	Free base, 137 – 139°	65.0 (65.3	8.0 7.8	14.7 14.5)
11	$-CH_2CH_2N(CH_3)CO(CH_2)_2CH_3$	Oxalate, 172 – 174°	57.8 (58.8	7.0 7.0	11.3 11.4)
12	$-CH_2CH_2N(CH_3)SO_2$.benzyl	Hydrochloride monohydrate, 169 – 172°	55.7 (55.7	6.3 6.5	10.0 10.4)
13	$-CH_2N(CH_3)CONH(CH_2)_3CH_3$	Free base, 154 – 157°	63.8 (63.6	7.8 8.0	16.7 16.9)
14	$-CH_2CH_2N(CH_3)SO_2(CH_2)_2CH_3$	Free base, 132 – 134°	57.6 (57.8	7.5 7.4	12.4 12.8)
15	$-CH(CH_3)CH_2N(CH_3)SO_2C_2H_5$	Oxalate, 159 – 161°	52.1 (52.5	6.5 6.5	10.5 10.6)

EXAMPLE 16
Preparation of 6,7-dimethoxy-4-[4-(3-*n*-butylureidomethyl)piperidino]quinazoline

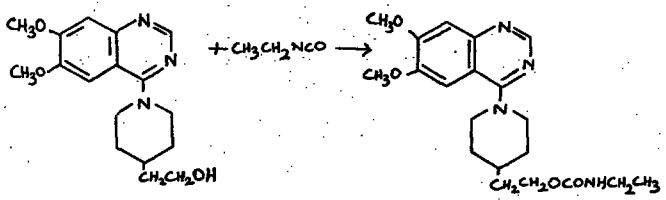


n-Butylisocyanate (1.8 g) was added to a stirred solution of 6,7-dimethoxy-4-[4-(amino-methyl)piperidino]quinazoline (5 g) in dry chloroform (100 ml). The mixture was then stirred at room temperature for 3 hours, then left standing for 72 hours. An equal volume of 1N hydrochloric acid was added, the organic phase separated, and the aqueous phase basified to pH 10 with aqueous potassium carbonate solution. The mixture was extracted with chloroform (2 x 100 ml), the extracts combined, dried ($MgSO_4$), and taken to dryness *in vacuo*. The resultant solid was recrystallised twice from acetonitrile and then once from a mixture of isopropanol and ether to yield 6,7-dimethoxy-4-[4-(3-*n*-butylureidomethyl)piperidino]quinazoline (3.3 g), m.p. 141—143°C.

Analysis %:—

Found:	C, 62.7; H, 7.8; N, 17.7
Calculated for $C_{21}H_{31}N_5O_3$:	C, 62.8; H, 7.8; N, 17.4.

EXAMPLE 17
Preparation of 6,7-Dimethoxy-4-[4-(2-N-ethylcarbamoyloxyethyl)piperidino]quinazoline



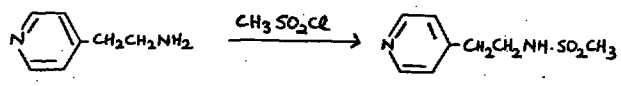
6,7-Dimethoxy-4-[4-(2-hydroxyethyl)piperidino]quinazoline (1.5 g) and ethyl isocyanate (4 g) were stirred together in dry chloroform (50 ml) at room temperature for 18 hours, then heated under reflux for 7 hours. The solution was cooled to room temperature and concentrated *in vacuo* to give a colourless oil which was dissolved in the minimum volume of chloroform and applied to the top of a chromatography column made up of 'Florisil' (Trade Mark) (100 g) in chloroform. The column was eluted with chloroform/5% methanol. 50 ml fractions were collected and monitored by thin layer chromatography. Appropriate fractions were combined and taken to dryness *in vacuo* to yield pure 6,7-dimethoxy-4-[4-(2-N-ethylcarbamoyloxyethyl)piperidino]quinazoline (0.8 g), m.p. 145°C.

Analysis %:—

Found:	C, 61.5; H, 7.5; N, 14.5
Calculated for $C_{20}H_{28}N_4O_4$:	C, 61.8; H, 7.3; N, 14.4.

The following Preparations, in which all temperatures are in °C illustrate the production of certain of the starting materials used in the previous Examples:—

PREPARATION 1
(A) Preparation of 4-(2-methanesulphonamidoethyl)pyridine



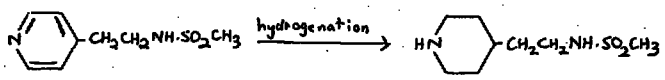
Methanesulphonyl chloride (3.5 g) was added slowly to 4-(2-aminoethyl)pyridine (3.6 g) and triethylamine (3.0 g) in chloroform (40 ml). The temperature was maintained below 40°C during the addition, after which the orange solution was left to stand at room temperature overnight. Water (50 ml) was then added, the chloroform phase was separated, and the aqueous phase extracted with chloroform (100 ml). The two chloroform solutions were combined, dried ($MgSO_4$) and taken to dryness *in vacuo* to give a yellow oil which solidified immediately. This solid was crystallised from ethanol to yield white crystals of 4-(2-methanesulphonamidoethyl)pyridine (1.4 g).

A small sample was recrystallised from ethanol, m.p. 114—116°C.

Analysis %:—

Found:	C, 47.9; H, 6.0; N, 14.0
Calculated for $C_8H_{12}N_2O_2S$:	C, 48.0; H, 6.0; N, 14.0.

(B) Preparation of 4-(2-methanesulphonamidoethyl)piperidine



4-(2-Methanesulphonamidoethyl)pyridine (8.4 g) in ethanol (85 ml) was acidified to pH 2 with 2N HCl and hydrogenated at room temperature and a pressure of 50 p.s.i. over a platinum oxide catalyst until hydrogen uptake ceased. The catalyst was then removed by filtration and the filtrate was taken to dryness *in vacuo* to give a white solid which was dissolved in the minimum volume of hot ethanol, filtered quickly, and left at room temperature overnight. The resultant white crystals were collected by filtration and dried to yield4-(2-methanesulphonamidoethyl)piperidine:hydrochloride (8.3 g), m.p. 165—167°C.

Analysis %:—

Found: C, 39.6; H, 7.8; N, 11.7

Calculated for $C_8H_{18}N_2O_2S$:HCl: C, 39.6; H, 7.9; N, 11.5.

Also synthesised in a similar fashion to Part (A) using the appropriate sulfonyl chloride or acid chloride were:

4-(2-[N-*iso*Propyl-methanesulphonamido]ethyl)pyridine oxalate, m.p. 129—131°, Found: C, 46.7; H, 6.2; N, 8.0%, $C_{11}H_{18}N_2O_2S$. $C_2H_2O_4$ requires: C, 47.0; H, 6.1; N, 8.4%;
4-(2-[N-Methyl-methanesulphonamido]ethyl)pyridine—crude oil;
(4-(2-Benzenesulphonamidoethyl)pyridine, m.p. 109—110°, Found: C, 59.5; H, 5.4; N, 10.6%, $C_{13}H_{14}N_2O_2S$ requires: C, 59.5; H, 5.4; N, 10.7%;
dl-4-(1-[N-Methyl-methanesulphonamido]prop-2-yl)pyridine oxalate, m.p. 155—158°;
4-(2-[N-Methyl-phenylmethanesulphonamido]ethyl pyridine, m.p. 109—110°, Found: C, 62.0; H, 6.3; N, 9.7%, $C_{15}H_{18}N_2O_2S$ requires: C, 62.1; H, 6.3; N, 9.7%;
4-(2-[N-Methyl-propanesulphonamido]ethyl)pyridine;
dl-4-(1-[N-Methyl-ethanesulphonamido]prop-2-yl)pyridine, and
4-(2-[N-Methyl-butyramido]ethyl)pyridine.

The above were then hydrogenated similarly to Part (B) to give the corresponding piperidines.

PREPARATION 2

(A) 4-(3-n-Butyl-1-methylureidomethyl)pyridine

4-(N-Methylaminomethyl)pyridine (3.6 g) in dry chloroform (70 ml) was stirred and cooled in an ice bath whilst *n*-butylisocyanate (9.9 g) was added slowly, dropwise.

The mixture was then allowed to stand at ambient temperature overnight after which methanol (15 ml) was added and stirring continued for a further 30 minutes. The solvents were removed by evaporation to dryness *in vacuo* and the residue was re-dissolved in ethyl acetate (50 ml). The oxalate salt was precipitated by treating the solution with a slight excess of oxalic acid in ethyl acetate. Recrystallisation from *iso*propanol gave pure 4-(3-*n*-butyl-1-methylureidomethyl)pyridine sesqui-oxalate (7.2 g), m.p. 86—90°.

Analysis %:—

Found: C, 50.4; H, 6.6; N, 11.9

$C_{12}N_{19}N_3O.1\frac{1}{2}(C_2H_2O_4)$ requires: C, 50.6; H, 6.2; N, 11.8.

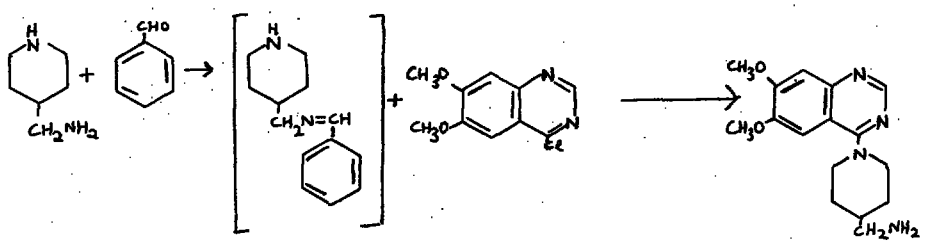
Also synthesised by a similar method were:

4-(2-[3-Ethylureido]ethyl)pyridine—crude base, unpurified
4-[1-Methyl-3-*n*-propylureidomethyl]pyridine—crude base, unpurified
4-(2-[3-Ethyl-1-methylureido]ethyl)pyridine—crude base, unpurified

(B) The above pyridines were then hydrogenated to the corresponding piperidines similarly to Preparation 1(B).

PREPARATION 3

(A) Preparation of 6,7-dimethoxy-4-[4-(aminomethyl)piperidino]quinazoline



4-(Aminomethyl)piperidine (11.4 g) and benzaldehyde (10.6 g) in benzene (200 ml) were heated under reflux in a flask fitted with a Dean and Stark water-trap. Although liberation of water had virtually

ceased after 4 hours, heating was continued for a further 8 hours. The benzene was then removed *in vacuo* to give an oil.

The above preparation was repeated on the same scale and the two products were combined to give crude 4-(benzylideneaminomethyl)piperidine (22.5 g).

Crude 4-(benzylideneaminomethyl)piperidine (20 g) and 4-chloro-6,7-dimethoxy quinazoline (22.5 g) in dimethylacetamide (500 ml) were allowed to stand together at room temperature for 72 hours.

The mixture was then taken to dryness *in vacuo* to give a solid which was triturated with ether (150 ml) and filtered. The ether filtrate was taken to dryness *in vacuo*, the resultant oil was heated at 95°C for 1½ hours with concentrated HCl (10 ml), diluted with water (20 ml) and extracted with chloroform (2 x 100 ml). The chloroform extract was washed with water (2 x 20 ml) and the aqueous washings were combined with the diluted acid solution remaining from the chloroform extraction and basified to pH 11 with aqueous sodium hydroxide. The basic solution was then extracted with chloroform (2 x 100 ml) and the extracts were dried ($MgSO_4$)—Solution A.

The solid collected from trituration with ether was stirred with chloroform and filtered. The chloroform filtrate was treated in the same manner as the previous ether filtrate to give Solution B.

Solutions A and B were combined, taken to dryness *in vacuo* and crystallised from methylcyclohexane to yield 6,7-dimethoxy-4-[4-(aminomethyl)piperidino]quinazoline (11 g), m.p. 144—146°C.

Analysis %:—

Found:	C, 63.3; H, 7.3; N, 17.8
Calculated for $C_{16}H_{22}N_4O_2$:	C, 63.6; H, 7.3; N, 18.5.

PREPARATION 4

dl-4-(1-[N-Methylacetamido]prop-2-yl)pyridine

dl-4-(1-Methylaminoprop-2-yl)pyridine (4.5 g) in acetic acid (15 ml) was treated cautiously with acetic anhydride (10 ml) followed by allowing the mixture to stand at ambient temperature overnight. Methanol (20 ml) was then added to destroy excess acetic anhydride, followed by evaporation *in vacuo* (at 40°C) to remove methanol and methyl acetate. The residue was diluted with water and treated portionwise with sodium carbonate (anhydrous) until alkaline (pH 10—12). The oily suspension was extracted with chloroform (3 x 60 ml) and the bulked extracts were dried (Na_2CO_3) and evaporated to dryness *in vacuo* to give a near-colourless oil (6.8 g). The oil was distilled to give pure dl-4-(1-[N-methylacetamido]prop-2-yl)pyridine (3 g), b.p. 138—140°/0.4 mm Hg. as a colourless oil).

Analysis %:—

Found:	C, 65.8; H, 8.5; N, 14.2
$C_{11}H_{16}N_2O.\frac{1}{2}H_2O$ requires:	C, 65.7; H, 8.5; N, 13.9.

The following compound was synthesised by a similar method:

4-(Acetamidomethyl)pyridine, m.p. 83—88°.

The above were then hydrogenated similarly to Example 1(B) to give the corresponding piperidines.

PREPARATION 5

4-(2-*iso*propylaminoethyl)pyridine

4-Vinylpyridine (21 g), *iso*propylamine (24 g), concentrated hydrochloric acid (40 g) and water (100 ml) were mixed together with cooling and then boiled under reflux for 20 hours. The mixture was cooled, basified to pH 12—13 (20% NaOH) and extracted with chloroform (3 x 200 ml). The bulked extracts were washed with water (100 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a green oil. The oil was distilled and the fraction boiling at 84—90°C/1 mm was collected (16.5 g) and identified (by n.m.r. spectroscopy) as 4-(2-isopropylaminoethyl)pyridine.

Also synthesised by a similar route were:

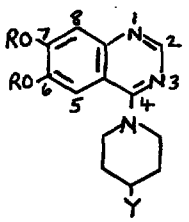
4-(2-Aminoethyl)pyridine

4-(2-Methylaminoethyl)pyridine, and

dl-4-(1-Methylaminoprop-2-yl)pyridine.

CLAIMS

1. A compound of the formula:



(I)

ceased after 4 hours, heating was continued for a further 8 hours. The benzene was then removed *in vacuo* to give an oil.

The above preparation was repeated on the same scale and the two products were combined to give crude 4-(benzylideneaminomethyl)piperidine (22.5 g).

Crude 4-(benzylideneaminomethyl)piperidine (20 g) and 4-chloro-6,7-dimethoxy quinazoline (22.5 g) in dimethylacetamide (500 ml) were allowed to stand together at room temperature for 72 hours.

The mixture was then taken to dryness *in vacuo* to give a solid which was triturated with ether (150 ml) and filtered. The ether filtrate was taken to dryness *in vacuo*, the resultant oil was heated at 95°C for 1½ hours with concentrated HCl (10 ml), diluted with water (20 ml) and extracted with chloroform (2 × 100 ml). The chloroform extract was washed with water (2 × 20 ml) and the aqueous washings were combined with the diluted acid solution remaining from the chloroform extraction and basified to pH 11 with aqueous sodium hydroxide. The basic solution was then extracted with chloroform (2 × 100 ml) and the extracts were dried ($MgSO_4$)—Solution A.

The solid collected from trituration with ether was stirred with chloroform and filtered. The chloroform filtrate was treated in the same manner as the previous ether filtrate to give Solution B.

Solutions A and B were combined, taken to dryness *in vacuo* and crystallised from methylcyclohexane to yield 6,7-dimethoxy-4-[4-(aminomethyl)piperidino]quinazoline (11 g), m.p. 144—146°C.

Analysis %:—

Found:	C, 63.3; H, 7.3; N, 17.8
Calculated for $C_{16}H_{22}N_4O_2$:	C, 63.6; H, 7.3; N, 18.5.

PREPARATION 4

dl-4-(1-[N-Methylacetamido]prop-2-yl)pyridine

dl-4-(1-Methylaminoprop-2-yl)pyridine (4.5 g) in acetic acid (15 ml) was treated cautiously with acetic anhydride (10 ml) followed by allowing the mixture to stand at ambient temperature overnight. Methanol (20 ml) was then added to destroy excess acetic anhydride, followed by evaporation *in vacuo* (at 40°C) to remove methanol and methyl acetate. The residue was diluted with water and treated portionwise with sodium carbonate (anhydrous) until alkaline (pH 10—12). The oily suspension was extracted with chloroform (3 × 60 ml) and the bulked extracts were dried (Na_2CO_3) and evaporated to dryness *in vacuo* to give a near-colourless oil (6.8 g). The oil was distilled to give pure dl-4-(1-[N-methylacetamido]prop-2-yl)pyridine (3 g), b.p. 138—140°/0.4 mm Hg. as a colourless oil).

Analysis %:—

Found:	C, 65.8; H, 8.5; N, 14.2
$C_{11}H_{16}N_2O.\frac{1}{2}H_2O$ requires:	C, 65.7; H, 8.5; N, 13.9.

The following compound was synthesised by a similar method:

4-(Acetamidomethyl)pyridine, m.p. 83—88°.

The above were then hydrogenated similarly to Example 1(B) to give the corresponding piperidines.

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Also synthesised by a similar route were:

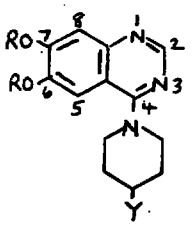
4-(2-Aminoethyl)pyridine

4-(2-Methylaminoethyl)pyridine, and

dl-4-(1-Methylaminoprop-2-yl)pyridine.

CLAIMS

1. A compound of the formula:



(I)

wherein R is a lower alkyl group;
and Y represents a group of the formula:

$$—(CHR^1)_m—Z$$

wherein R^1 is a hydrogen atom or a lower alkyl group, and m is 1 or 2, with the proviso that when m is 2, each R^1 may be the same or different;
and
Z is a group selected from:

$—OCONR^4R^5$

$—N(R^2)COR^3$

$—N(R^2)SO_2R^3$

and $—N(R^2)CONR^4R^5$

wherein R^2 is hydrogen or lower alkyl, R^3 is lower alkyl, benzyl, or phenyl, and R^4 and R^5 are each independently hydrogen or a group as defined for R^3 above; and the pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 wherein R is methyl.

3. A compound as claimed in claim 1 or 2 wherein $—(CHR^1)_m—$ is $—CH_2—$, $—CH_2CH_2—$, or $—CH(CH_3)CH_2—$.

4. A compound as claimed in any one of the preceding claims wherein Z is:

(a) $—OCONHR^5$ wherein R^5 is a $C_1—C_4$ alkyl group;
(b) $—N(R^2)COR^3$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^3 is a $C_1—C_4$ alkyl group;
(c) $—N(R^2)SO_2R^3$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^3 is $C_1—C_4$ alkyl, phenyl or benzyl; *or*
(d) $—N(R^2)CONHR^5$ wherein R^2 is hydrogen or $C_1—C_4$ alkyl, and R^5 is a $C_1—C_4$ alkyl group.

5. A compound as claimed in claim 1 wherein R is methyl and Y is either:

$—CH_2CH_2OCONHC_2H_5$,

$—CH_2CH_2NHSO_2CH_3$,

$—CH_2CH_2N(CH_3)SO_2CH_3$,

$—CH_2N(CH_3)CONH(CH_2)_2CH_3$,

$—CH_2CH_2N(CH[CH_3]_2)SO_2CH_3$,

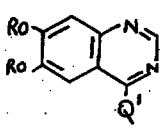
$—CH(CH_3)CH_2N(CH_3)SO_2CH_3$,

$—CH(CH_3)CH_2N(CH_3)COCH_3$,

$—CH_2N(CH_3)CONH(CH_2)_3CH_3$,

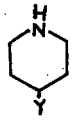
or $—CH(CH_3)CH_2N(CH_3)SO_2C_2H_5$.

6. A process for preparing a compound of the formula (I) as claimed in claim 1, which comprises reacting a quinazoline of the formula:



(II)

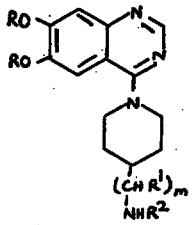
wherein R is lower alkyl and Q^1 is a facile leaving group, with an amine of the formula:



(III)

wherein Y is as defined in claim 1.

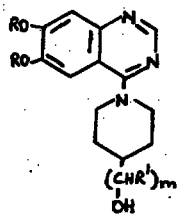
7. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Z is —N(R^2)CONHR^5, which comprises reacting a quinazoline of the formula:



(IV)

wherein R, R^1, R^2 and m are as defined in claim 1, with an isocyanate of the formula R^5NCO, R^5 being as defined in claim 1 other than hydrogen, or, to prepare compounds in which R^5 is H, sodium or potassium cyanate in the presence of acid.

8. A process for preparing a compound of the formula (I) as claimed in claim 1 wherein Z is —OCONHR^5, which comprises reacting a quinazoline of the formula:



(V)

wherein R, R^1 and m are as defined in claim 1, with an isocyanate of the formula R^5NCO, R^5 being as defined in claim 1 other than hydrogen, or, to prepare compounds in which R^5 is hydrogen, sodium or potassium cyanate in the presence of acid.

9. A process as claimed in claim 6 substantially as hereinbefore described in any one of Examples 1 to 15.

10. A process as claimed in claim 7 substantially as hereinbefore described in Example 16.

11. A process as claimed in claim 8 substantially as hereinbefore described in Example 17.

12. A compound of the formula (I) as claimed in claim 1 which has been prepared by a process as claimed in any one of claims 6 to 11.

13. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of claims 1 to 5 and 12, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier.

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