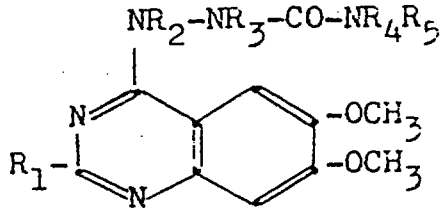
21L 149-091

The invention relates to new semicarbazides, the preparation thereof by methods known per se and their use as therapeutic active substances.

The new compounds correspond to formula I



(I)

wherein (and in the following formulae)

$R_1$ represents hydrogen, $C_{1-4}$ alkyl or trifluoromethyl,

$R_2$, $R_3$ and $R_4$ represent hydrogen, methyl or ethyl,

$R_5$ represents hydrogen, optionally phenyl-substituted $C_{1-8}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{1-4}$ alkoxycarbonylmethyl, phenyl, naphthyl, a phenyl or naphthyl group mono- to trisubstituted by methyl, ethyl, methoxy, ethoxy, trifluoromethyl, fluorine, chlorine or bromine,

$R_4$ and $R_5$ together also represent an alkylene chain with 4 or 5 chain members, optionally interrupted by O or $NR_6$, and

$R_6$ represents a $C_{1-4}$ alkyl.

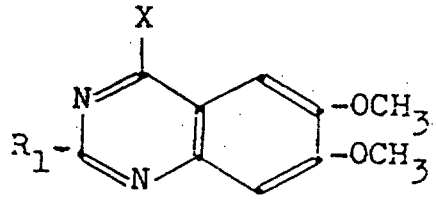
They may occur in the form of the free bases or as salts with acids.

The alkyl groups in the groups defined above may be straight-chained or branched. If $R_1$ to $R_4$ represent alkyl, this is preferably methyl or ethyl. In the case of $R_5$, the alkyl group preferably has 3 to 5 carbon atoms and the cycloalkyl group has 5 to 6 carbon atoms, whilst the alkoxy group

in the alkoxycarbonylmethyl group is preferably methoxy or ethoxy. The substituents in the aromatic groups are methyl, ethyl, methoxy, ethoxy, fluorine, chlorine, bromine and $CF_3$. Methyl, methoxy and chlorine should be particularly emphasised. Up to three identical or different substituents may be present. If $R_4$ and $R_5$ represent an alkylene chain optionally interrupted by O or $NR_6$, they may, for example, represent a group such as $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-CH_2-$ or $-CH_2-CH_2-NCH_3-CH_2-CH_2-$. The group $R_1$ preferably represents H and $CH_3$. The substituents $R_2$, $R_3$ and $R_4$ preferably represent H.

The new compounds may be obtained by the following processes:

a) A 6,7-dimethoxyquinazoline of formula II



(II)

wherein X represents a group, preferably chlorine, which can be exchanged for the nitrogen of the semicarbazide of formula III

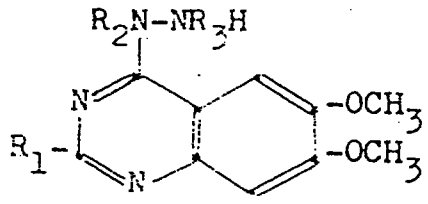
$$HNR_2-NR_3-CO-NR_4R_5 \qquad \text{(III)},$$

is reacted with the semicarbazide III in a solvent which is inert under the reaction conditions.

Suitable solvents include, for example, dimethylformamide, acetonitrile, tetrahydrofuran and alcohols. Depending on the reactivity of the components, the reaction is carried out at temperatures of between ambient temperature and the boiling temperature of the reaction mixture, preferably between 40

and 120°C, in the presence of a basic substance, e.g. sodium carbonate, potassium carbonate or a tertiary amine.

b) A quinazoline of formula IV



(IV)

is reacted with an isocyanate of formula V

$$OCN-R_5 \qquad (V)$$

in a solvent which is inert under the reaction conditions, to yield compounds of formula I wherein $R_4$ represents hydrogen.

The reaction is carried out in solvents such as tetrahydrofuran, dioxan, ether, dimethylformamide, toluene, acetone or acetonitrile, preferably at ambient temperature or with gentle heating. The compound of formula IV may be present as a suspension.

c) Compounds of formula IV are reacted with carbamoyl chlorides of formula VI

$$R'_4R'_5N-COCl \qquad (VI)$$

(wherein $R'_4$ and $R'_5$ have the same meanings as $R_4$ and $R_5$, with the exception of hydrogen) in a solvent which is inert under the reaction conditions. Compounds of formula I are thus obtained wherein $R_4$ and $R_5$ are as hereinbefore defined but cannot represent hydrogen.

The solvents mentioned under process b), particularly dimethylformamide, are suitable for

(31)

this process. An acid-binding agent, such as potassium or sodium carbonate, a tertiary organic base or an excess of amine is conveniently used.

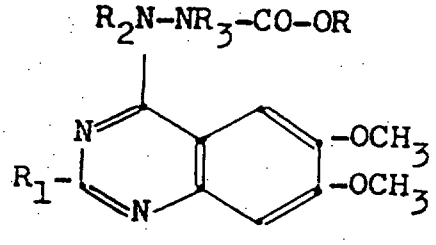
d) A compound of formula IV is reacted with a substituted carbaminic acid ester of formula VII

$$R_4R_5\text{-N-COOR} \qquad \text{(VII)}$$

wherein R represents an optionally substituted saturated or unsaturated aliphatic or araliphatic group, at elevated temperature in a solvent which is inert under the reaction conditions.

The solvent may be, for example, acetone, dimethylformamide or an alcohol. The reaction temperature is generally between 40 and 80°C. If solvents with a suitable boiling point, such as methanol, are used, the reaction may be carried out at reflux temperature.

e) A compound of formula VIII




(VIII)

is reacted with a primary or secondary amine of formula IX

$$HNR_4R_5 \qquad \text{(IX)}$$

at elevated temperature in a solvent which is inert under the reaction conditions.

In this process, the solvent and reaction temperatures mentioned under d) may be used.

If salts are obtained as the reaction products, these may, if desired, be converted into the bases of formula I or into salts of other acids. Bases obtained initially may, if desired, be converted into acid addition salts in the usual way. The starting materials are known or else may be obtained by conventional methods.

The compounds according to the invention are suitable as active substances for pharmaceutical compositions. The compounds are, in particular, phosphodiesterase inhibitors and heart stimulants with a long-lasting activity. They increase the contractile force of the heart muscle without significantly affecting the heart rate.

This selectivity, in particular, makes them useful for the therapeutic and prophylactic treatment of pathological heart conditions, particularly heart failure. Apart from their effect on heart muscle, the compounds according to the invention also have vasodilatory and hypotensive properties and in some cases they increase the circulation of blood through the kidneys and broncholysis. The therapeutic and prophylactic dose depends on the nature and gravity of the complaint and on the method of administration.

For administration to adults, the oral doses are within the range from 20 to 1000 mg per day, generally divided up into 2 to 4 units. For intravenous administration, the individual dose is between 1 and 300 mg.

The substances may be administered in the usual forms, e.g. capsules, tablets, coated tablets, solutions, suspensions for oral administration and sterile aqueous isotonic solutions for parenteral administration.

The pharmaceutical preparations contain excipients and/or carriers conventionally used in galenic pharmacy, together with the active substances according

to the invention and optionally other therapeutically active substances.

Examples of formulation:

Tablets

Composition:

| | |
|---|---|
| Active substance according to the invention | 100 mg |
| Colloidal silicic acid | 10 mg |
| Lactose | 118 mg |
| Potato starch | 60 mg |
| Polyvinylpyrrolidone | 6 mg |
| Sodium cellulose glycolate | 4 mg |
| Magnesium stearate | 2 mg |
| | 300 mg |

The ingredients are processed in the usual way to form 300 mg tablets each of which contains 100 mg of the active substance according to the invention. If desired, suitable quantities of known active substances may be combined with the ingredients stated.

Capsules

Composition:

| | |
|---|---|
| Active substance according to the invention | 200 mg |
| Corn starch | 200 mg |

The ingredients are thoroughly mixed in the ratios mentioned above and packed into gelatine capsules in amounts of 400 mg.

Example 1

1-(6,7-Dimethoxyquinazol-4-yl)-semicarbazide

2.2 g of 6,7-dimethoxy-4-chloro-quinazoline are dissolved in 50 ml of absolute dimethylformamide. 2.2 g of semicarbazide x HCl and 5 g of anhydrous potash are added thereto, with stirring. The mixture is stirred for 5 hours at 50°C and the precipitate is suction filtered. It is stirred with water and then recrystallised from dimethylformamide. The crude product is obtained in a 30% yield; m.p. 247-249°C.

Example 2

1-n-Butyl-4-(6,7-dimethoxyquinazol-4-yl)-semicarbazide-hydrochloride

3 g of 6,7-dimethoxy-4-chloro-quinazoline are stirred with 3.5 g of 4-n-butylsemicarbazide in 100 ml of n-amyl alcohol for 2 hours at 100°C. Then the precipitate is suction filtered, suspended while hot in alcohol and brought to pH 5 by the addition of 2N hydrochloric acid. The clear solution is filtered over charcoal, cooled, suction filtered and dried in a circulating air drier. The hydrochloride of 4-n-butyl-4-(6,7-dimethoxyquinazol-4-yl)-semicarbazide, which is obtained in a 70% yield, melts at 216-217°C.

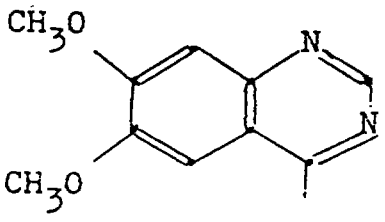
The following are obtained accordingly:

1-n-Butyl-4-(6,7-dimethoxy-2-trifluoromethylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 210-212°C).

1-n-Butyl-4-(6,7-dimethoxy-2-methylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 295-297°C).

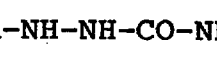
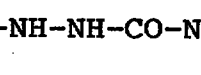
(36)

The following compounds are also obtained analogously:

R = 

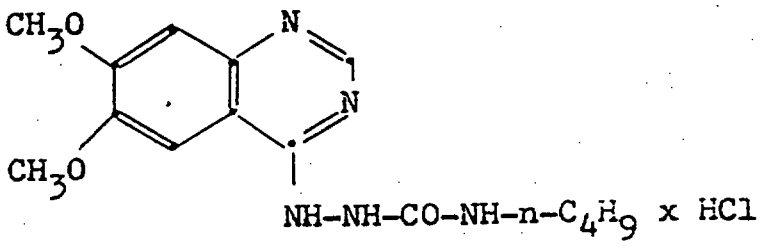
| | Yield [in % of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$CH_2$-$COOCH_3$ x HCl | 48 | 214-5 |
| R-NH-NH-CO-NH-$CH_3$ x HCl | 89 | 246-7 |
| R-N(-$CH_3$)-NH-CO-NH-n-$C_4H_9$ x HCl | 52 | 207-8 |
| R-N(-$CH_3$)-N(-$CH_3$)-CO-NH-n-$C_4H_9$ x HCl | 30 | 203-4 |
| R-NH-NH-CO-NH-$C(CH_3)_3$ x HCL | 43 | 296-7 |
| R-NH-NH-CO-NH-$C_6H_5$ x HCl | 57 | 199 |
| R-NH-NH-CO-NH-(4-Cl-$C_6H_4$) | 59 | 198-199 |
| R-NH-NH-CO-NH-(3-$CH_3$-$C_6H_4$) | 55 | 194-95 |
| R-NH-N(-$CH_3$)-CO-NH-$C_4H_9$ | 35 | 210-211 |
| R-NH-NH-CO-N(CH$_2$-CH$_2$-O-CH$_2$-CH$_2$) x HCl | 35 | 248-51 |
| R-NH-NH-CO-N$(CH_3)_2$ x HCl | 40 | 246-48 |
| R-NH-NH-CO-N(CH$_2$-CH$_2$-N(-$CH_3$)-CH$_2$-CH$_2$) x HCl | 36 | 287-88 |
| R-NH-NH-CO-N$(i\text{-}C_3H_7)_2$ | 38 | 256-57 |

37

| | Yield [in % of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$(CH_2)_5$-$CH_3$ x HCl | 73 | 213-214 |
| R-NH-NH-CO-NH-$(CH_2)_4$-$CH_3$ x HCl | 49 | 210-211 |
| R-NH-NH-CO-NH-CH$(CH_3)$-$C_6H_5$ x HCl | 53 | 212 |
| R-NH-NH-CO-NH-$CH_2$-$C_6H_5$ x HCl | 79 | 210-211 |
| R-NH-NH-CO-NH-CH$(CH_3)$-$C_3H_7$ x HCl | 56 | 204 |
| R-NH-NH-CO-NH-CH$(C_2H_5)_2$ x HCl | 76 | 218-219 |
| R-NH-NH-CO-NH-$CH_2$-C$(CH_3)_3$ x HCl | 84 | 208 |
| R-NH-NH-CO-NH-CH$(CH_3)$-CH$(CH_3)_2$ x HCl | 77 | 197-199 |
| R-NH-NH-CO-NH-$C_2H_5$ x HCl | 80 | 226-227 |
| R-NH-NH-CO-NH-CH$(CH_3)_2$ x HCl | 81 | 220-221 |
| R-NH-NH-CO-NH-$(CH_2)_7$-$CH_3$ x HCl | 83 | 208-209 |
| R-NH-NH-CO-NH- x HCl | 75 | 207-209 |
| R-NH-NH-CO-NH- x HCl | 82 | 200-201 |
| R-NH-NH-CO-NH-n-$C_4H_9$ x HCl | 69 | 295-297 |

Example 3

1-n-Butyl-4-(6,7-dimethoxyquinazolin-4-yl)-semicarbazide-hydrochloride




5.12 g of 6,7-Dimethoxy-4-hydrazino-quinazoline are partially dissolved in 200 ml of absolute acetonitrile. Then 5 ml of n-butylisocyanate are added thereto, all in one go. As the temperature rises slightly, a solution is rapidly obtained. This is stirred for a further 4 hours and then left to stand overnight. The precipitate is suction filtered, dissolved while hot in ethanol and mixed with the calculated quantity of ethanolic hydrochoric acid. The hydrochloride of 1-n-butyl-4-(6,7-dimethoxy-quinazolin-4-yl)-semicarbazide crystallises out. After cooling, it is suction filtered and dried in a circulating air drier. The end product, which is obtained in a 60% yield, has a melting point of 216-217°C.

Example 4

1-n-Butyl-4-(6,7-dimethoxy-2-methylquinazol-4-yl)-semicarbazide-hydrochloride

a) 2.2 g of 6,7-dimethoxy-4-hydrazino-2-methylquinazoline are suspended in 100 ml of absolute acetonitrile. 2 g of butylisocyanate are added all in one go and the mixture is stirred for 3 hours at ambient temperature. The base is suction filtered and dissolved in alcohol, then the calculated quantity of ethereal hydrochloric acid is added.

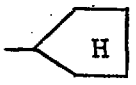
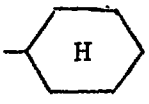
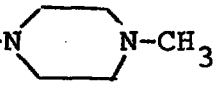
The hydrochloride precipitated (2.3 g, 66% of theory) is suction filtered and dried in a drying cupboard (Mp. 295-297°C).

b) The 6,7-dimethoxy-4-hydrazino-2-methyl-quinazoline (Mp. 227-229°C) needed as a starting material is obtained by reacting 4-chloro-6,7-dimethoxy-2-methyl-quinazoline with excess hydrazine in dimethylformamide.

Using the same procedure, 1-n-butyl-4-(6,7-dimethoxy-2-trifluoromethylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 210-212°C) is also prepared in a 73% yield.

The following are synthesised analogously to these Examples:
(R represents 6,7-dimethoxyquinazolin-4-yl)

| | Yield in % [of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$CH_2$-$COOCH_3$ x HCl | 48 | 214-215 |
| R-NH-NH-CO-NH-$CH_3$ x HCl | 89 | 246-247 |
| R-N($CH_3$)-NH-CO-NH-$C_4H_9$ x HCl | 52 | 207-208 |
| R-N($CH_3$)——N($CH_3$)-CO-NH-$C_4H_9$ x HCl | 30 | 203-204 |
| R-NH-NH-CO-NH-$C(CH_3)_3$ x HCl | 43 | 296-297 |
| R-NH-NH-CO-NH-$C_6H_5$ x HCl | 57 | 199 |
| R-NH-NH-CO-NH-4-Cl-$C_6H_4$ | 63 | 198-199 |
| R-NH-NH-CO-NH-3-$CH_3$-$C_6H_4$ | 70 | 194-195 |
| R-NH-N($CH_3$)-CO-NH-$C_4H_9$ | 62 | 210-211 |
| R-NH-NH-CO-$NH_2$ x HCl | | 247-249 |
| R-NH-NH-CO-NH-$C_2H_5$ x HCl | 76 | 226-227 |
| R-NH-NH-CO-NH-$CH(CH_3)_2$ x HCl | 87 | 220-221 |
| R-NH-NH-CO-NH-n-$C_5H_{11}$ x HCl | 50 | 210-211 |
| R-NH-NH-CO-NH-$CH(CH_3)$-n-$C_3H_7$ x HCl | 53 | 204 |
| R-NH-NH-CO-NH-$CH(C_2H_5)_2$ x HCl | 84 | 218-219 |

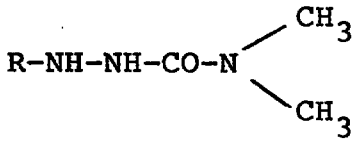
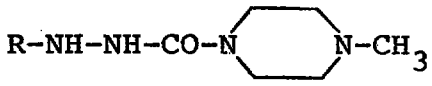
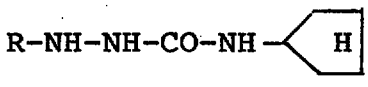
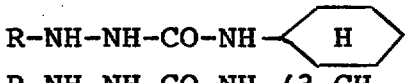
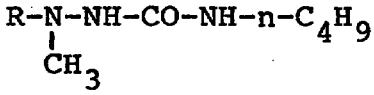
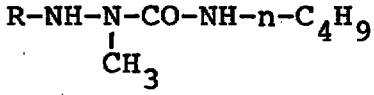
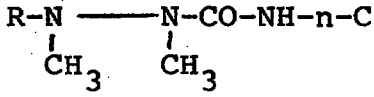
| | Yield in % [of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$CH_2$-$C(CH_3)_3$ x HCl | 80 | 208 |
| R-NH-NH-CO-NH-$CH(CH_3)$-$CH(CH_3)_2$ x HCl | 73 | 197-199 |
| R-NH-NH-CO-NH-n-$C_6H_{13}$ x HCl | 70 | 213-214 |
| R-NH-NH-CO-NH-n-$C_8H_{17}$ x HCl | 80 | 208-209 |
| R-NH-NH-CO-NH-$CH_2$-$C_6H_5$ x HCl | 85 | 210-211 |
| R-NH-NH-CO-NH-$CH(CH_3)$-$C_6H_5$ x HCl | 59 | 212 |
| R-NH-NH-CO-NH- x HCl | 72 | 200-201 |
| R-NH-NH-CO-NH- x HCl | 70 | 207-209 |
| R-NH-NH-CO-$N(CH_3)_2$ x HCl | | 246-248 |
| R-NH-NH-CO-$N(iC_3H_7)_2$ x HCl | | 256-257 |
| R-NH-NH-CO- x HCl | | 248-251 |
| R-NH-NH-CO- | | 287-288 |

Example 5

6,7-Dimethoxy-4-(2-morpholinocarbonyl)-hydrazino-quinazoline-hydrochloride

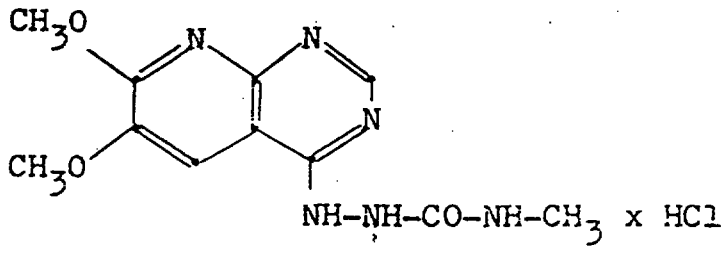
2.2 g of 6,7-Dimethoxy-4-hydrazino-quinazoline are dissolved in 20 ml of dimethylformamide. 2.76 g of anhydrous potash are added and then 1.7 g of morpholinocarbamidic acid chloride are added dropwise thereto, with stirring. The mixture is left to react for 2 hours at ambient temperature, then poured onto ice water and the precipitate is separated off by suction filtering. This precipitate is then dissolved in ethanol and converted into the hydrochloride by the addition of ethereal hydrochloric acid. After suction filtering and drying in the circulating air drier, the hydrochloride of 6,7-dimethoxy-4-(2-morpholinocarbonyl)-hydrazino-quinazoline is obtained in a 40% yield: m.p. 248-251°C.

The following were synthesised analogously to this Example:

| | Yield [in % of theory] | Mp.[°C] |
|---|---|---|
|  | 30 | 246-248 |
|  | 35 | 287-288 |
| R-NH-NH-CO-N-(i-$C_3H_7$)$_2$ | 38 | 256-257 |
| R-NH-NH-CO-$NH_2$ x HCl | | 247-249 |
| R-NH-NH-CO-NH-$C_2H_5$ x HCl | 76 | 226-227 |
| R-NH-NH-CO-NH-$CH(CH_3)_2$ x HCl | 87 | 220-221 |
| R-NH-NH-CO-NH-n-$C_4H_9$ x HCl | | 216-217 |
| R-NH-NH-CO-NH-$C(CH_3)_3$ x HCl | | 296-297 |
| R-NH-NH-CO-NH-n-$C_5H_{11}$ x HCl | 50 | 210-211 |
| R-NH-NH-CO-NH-$CH(CH_3)$-n-$C_3H_7$ x HCl | 53 | 204 |
| R-NH-NH-CO-NH-$CH(C_2H_5)_2$ x HCl | 84 | 218-219 |
| R-NH-NH-CO-NH-$CH_2$-$C(CH_3)_3$ x HCl | 80 | 208 |
| R-NH-NH-CO-NH-$CH(CH_3)$-$CH(CH_3)_2$ x HCl | 73 | 197-199 |
| R-NH-NH-CO-NH-n-$C_6H_{13}$ x HCl | 70 | 213-214 |
| R-NH-NH-CO-NH-n-$C_8H_{17}$ x HCl | 80 | 208-209 |
| R-NH-NH-CO-NH-$C_6H_5$ x HCl | | 199 |
| R-NH-NH-CO-NH-$CH_2$-$C_6H_5$ x HCl | 85 | 210-211 |
| R-NH-NH-CO-NH-$CH(CH_3)$-$C_6H_5$ x HCl | 59 | 212 |
|  | 72 | 200-201 |
|  | 70 | 207-209 |
| R-NH-NH-CO-NH-(3-$CH_3$-$C_6H_4$) x HCl | | 194-195 |
| R-NH-NH-CO-NH-(4-Cl-$C_6H_4$ x HCl | | 198-199 |
|  | | 207-208 |
|  | | 210-211 |
|  | | 203-204 |

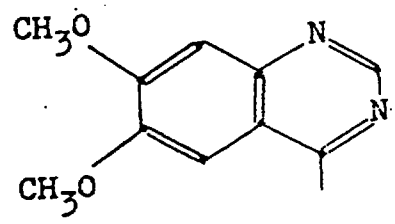
Example 6

1-Methyl-4-(6,7-dimethoxyquinazolin-4-yl)-semicarbazide-hydrochloride




2.2 g of 6,7-dimethoxy-4-hydrazino-quinazoline are suspended in 100 ml of methanol. After the addition of 1.8 g of methyl N-methylcarbaminate, the mixture is refluxed for 4 hours. The clear solution is cooled, the precitate is suction filtered, dissolved again in hot methanol and mixed with the calculated quantity of ethereal hydrochloric acid. This mixture is cooled and suction filtered and dried in the circulating air dryer. The hydrochloride of 1-methyl-4-(6,7-dimethoxyquinazolin-4-yl)-semicarbazide is obtained in a 50% yield; m.p. 246-247°C.

The following are obtained analogously:

R = 

| | Yield [in % of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$CH_2$-$COOCH_3$ x HCl | 48 | 214-215 |
| R-N(-$CH_3$)-NH-CO-NH-n-$C_4H_9$ x HCl | 52 | 207-208 |
| R-N(-$CH_3$)-N(-$CH_3$)-CO-NH-n-$C_4H_9$ x HCl | 30 | 203-204 |
| R-NH-NH-CO-NH-$C(CH_3)_3$ x HCl | 43 | 296-297 |
| R-NH-NH-CO-NH-$C_6H_5$ x HCl | 57 | 199 |
| R-NH-NH-CO-NH(4-Cl-$C_6H_4$) | 52 | 198-199 |
| R-NH-NH-CO-NH-(3-$CH_3$-$C_6H_4$) | 56 | 194-95 |
| R-NH-N(-$CH_3$)-CO-NH-$C_4H_9$ | 35 | 210-211 |
| R-NH-NH-CO-N(CH$_2$-CH$_2$-O-CH$_2$-CH$_2$) x HCl | 22 | 248-51 |
| R-NH-NH-CO-$N(CH_3)_2$ x HCl | 28 | 246-48 |
| R-NH-NH-CO-N(CH$_2$-CH$_2$-N($CH_3$)-CH$_2$-CH$_2$) x HCl | 35 | 287-88 |
| R-NH-NH-CO-$N(i\text{-}C_3H_7)_2$ | 36 | 256-57 |
| R-NH-NH-CO-$NH_2$ x HCl | | 247-249 |
| R-NH-NH-CO-NH-$C_2H_5$ x HCl | | 226-227 |
| R-NH-NH-CO-NH-$CH(CH_3)_2$ x HCl | | 220-221 |
| R-NH-NH-CO-NH-n-$C_4H_9$ x HCl | | 216-217 |
| R-NH-NH-CO-NH-n-$C_5H_{11}$ x HCl | | 210-211 |

| | Mp.[°C] |
|---|---|
| R-NH-NH-CO-NH-CH($CH_3$)-$C_3H_7$ x HCl | 204 |
| R-NH-NH-CO-NH-CH($C_2H_5$)$_2$ x HCl | 218-219 |
| R-NH-NH-CO-NH-$CH_2$-C($CH_3$)$_3$ x HCl | 208 |
| R-NH-NH-CO-NH-CH($CH_3$)-CH($CH_3$)$_2$ x HCl | 197-199 |
| R-NH-NH-CO-NH-n-$C_6H_{13}$ x HCl | 213-214 |
| R-NH-NH-CO-NH-n-$C_8H_{17}$ x HCl | 208-209 |
| R-NH-NH-CO-NH-$CH_2$-$COOCH_3$ x HCl | 214-215 |
| R-NH-NH-CO-NH-$CH_2$-$C_6H_5$ x HCl | 210-211 |
| R-NH-NH-CO-NH-CH($CH_3$)-$C_6H_5$ x HCl | 212 |
| R-NH-NH-CO-NH- | 200-201 |
| R-NH-NH-CO-NH- | 207-209 |

Moreover, the following are obtained accordingly: 1-n-Butyl-4-(6,7-dimethoxy-2-trifluoromethylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 210-212°C).

1-n-Butyl-4-(6,7-dimethoxy-2-methylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 295-297°C).

Example 7

1-Methyl-4-(6,7-dimethoxyquinazolin-4-yl)-semicarbazide-hydrochloride

1.5 g of 6,7-dimethoxy-4-(2-carbethoxy)-hydrazino-quinazoline, which may be obtained by reacting 6,7-dimethoxy-4-hydrazino-quinazoline with ethyl chlorocarbonate, are dissolved in 30 ml of dioxan. After the addition of 2 ml of 40% methylamine solution, the mixture is heated to 60°C for 3 hours. The crystals precipitated are suction filtered, suspended in alcohol while hot and then the calculated quantity of alcoholic hydrochloric acid is added. A solution is rapidly obtained. This is cooled, suction filtered and dried. The hydrochloride of 1-methyl-4-(6,7-

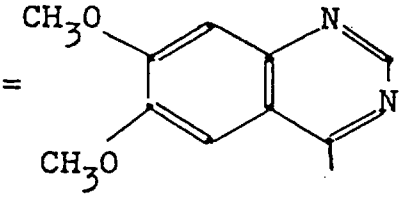
dimethoxyquinazolin-4-yl)-semicarbazide (Mp. 246-7°C) is obtained in a 20% yield.

The following are obtained analogously:

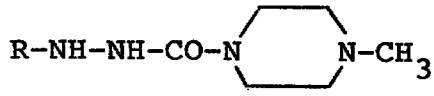
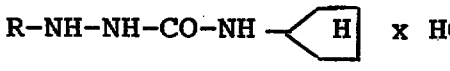
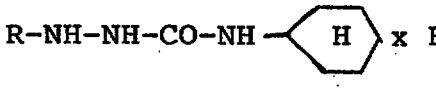
1-n-Butyl-4-(6,7-dimethoxy-2-trifluoromethylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 210-212°C).

1-n-Butyl-4-(6,7-dimethoxy-2-methylquinazol-4-yl)-semicarbazide-hydrochloride (Mp. 295-297°C).

The following are obtained analogously:

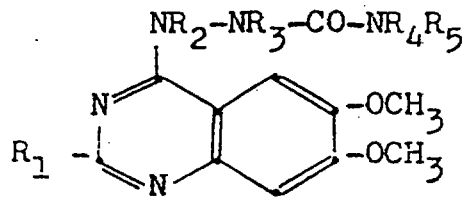
R = 

| | Yield [in % of theory] | Mp.[°C] |
|---|---|---|
| R-NH-NH-CO-NH-$CH_2$-$COOCH_3$ x HCl | 48 | 214-215 |
| R-N($CH_3$)-NH-CO-NH-n-$C_4H_9$ x HCl | 52 | 207-208 |
| R-N($CH_3$)-N($CH_3$)-CO-NH-n-$C_4H_9$ x HCl | 30 | 203-204 |
| R-NH-NH-CO-NH-$C(CH_3)_3$ x HCl | 43 | 296-297 |
| R-NH-NH-CO-NH-$C_6H_5$ x HCl | 57 | 199 |
| R-NH-NH-CO-NH-(4-Cl-$C_6H_4$) | 52 | 198-199 |
| R-NH-NH-CO-NH-(3-$CH_3$-$C_6H_4$) | 46 | 194-195 |
| R-NH-N($CH_3$)-CO-NH-$C_4H_9$ | 42 | 210-211 |
| R-NH-NH-CO-N(morpholine) x HCl | 35 | 248-251 |
| R-NH-NH-CO-N$(CH_3)_2$ x HCl | 30 | 246-248 |

| | | |
|---|---|---|
|  | 28 | 287-288 |
| $R-NH-NH-CO-N(i-C_3H_7)_2$ | 35 | 256-257 |
| $R-NH-NH-CO-NH_2 \times HCl$ | | 247-249 |
| $R-NH-NH-CO-NH-C_2H_5 \times HCl$ | 76 | 226-227 |
| $R-NH-NH-CO-NH-CH(CH_3)_2 \times HCl$ | 87 | 220-221 |
| $R-NH-NH-CO-NH-n-C_4H_9 \times HCl$ | | 216-217 |
| $R-NH-NH-CO-NH-n-C_5H_{11} \times HCl$ | 50 | 210-211 |
| $R-NH-NH-CO-NH-CH(CH_3)-n-C_3H_7 \times HCl$ | 53 | 204 |
| $R-NH-NH-CO-NH-CH(C_2H_5)_2 \times HCl$ | 84 | 218-219 |
| $R-NH-NH-CO-NH-CH_2-C(CH_3)_3 \times HCl$ | 80 | 208 |
| $R-NH-NH-CO-NH-CH(CH_3)-CH(CH_3)_2 \times HCl$ | 73 | 197-199 |
| $R-NH-NH-CO-NH-n-C_6H_{13} \times HCl$ | 70 | 213-214 |
| $R-NH-NH-CO-NH-n-C_8H_{17} \times HCl$ | 80 | 208-209 |
| $R-NH-NH-CO-NH-CH_2-C_6H_5 \times HCl$ | 85 | 210-211 |
| $R-NH-NH-CO-NH-CH(CH_3)-C_6H_5 \times HCl$ | 59 | 212 |
|  | 72 | 200-201 |
|  | 70 | 207-209 |

## Patent claims

1. Compounds of formula I



(I)

wherein

$R_1$ represents hydrogen, $C_{1-4}$ alkyl or trifluoromethyl,

$R_2$, $R_3$ and $R_4$ represent hydrogen, methyl or ethyl,

$R_5$ represents hydrogen, optionally phenyl-substituted $C_{1-8}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{1-4}$ alkoxycarbonylmethyl, phenyl, naphthyl, a phenyl or naphthyl group mono- to trisubstituted by methyl, ethyl, methoxy, ethoxy, trifluoromethyl, fluorine, chlorine or bromine,

$R_4$ and $R_5$ together also represent an alkylene chain with 4 or 5 chain members, optionally interrupted by O or $NR_6$, and

$R_6$ represents a $C_{1-4}$ alkyl, in the form of acid addition salts and in the form of free bases.

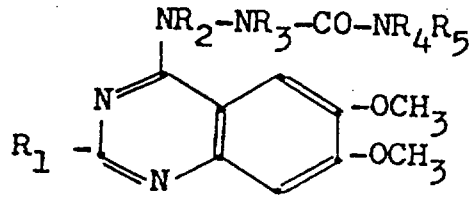
2. Compounds as claimed in claim 1, characterised in that $R_1$ represents hydrogen or methyl, $R_2$, $R_3$ and $R_4$ represent hydrogen, $R_5$ represents hydrogen, $C_{3-5}$ alkyl, $C_{5-6}$ cycloalkyl, methoxy- or ethoxycarbonylmethyl, phenyl, chlorophenyl, α- or β-naphthyl or benzyl, and $R_4$ and $R_5$ together represent $-CH_2CH_2-O-CH_2-CH_2-$ or $-CH_2-CH_2-NCH_3-CH_2-CH_2-$.

3. Pharmaceutical composition, characterised in that it contains a compound as claimed in claim 1 or 2 in addition to conventional excipients and/or carriers.

4. Use of compounds as claimed in claim 1 or 2 for the therapeutic or prophylactic treatment

of pathological heart conditions.

5. Process for preparing compounds of formula I



(I)

wherein

$R_1$ represents hydrogen, $C_{1-4}$ alkyl or trifluoromethyl,

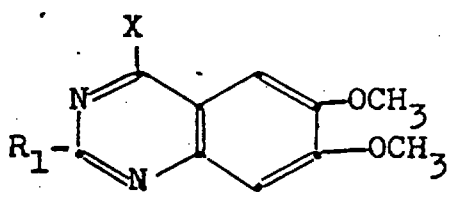
$R_2$, $R_3$ and $R_4$ represent hydrogen, methyl or ethyl,

$R_5$ represents hydrogen, optionally phenyl-substituted $C_{1-8}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{1-4}$ alkoxycarbonylmethyl, phenyl, naphthyl, a phenyl or naphthyl group mono- to trisubstituted by methyl, ethyl, methoxy, ethoxy, trifluoromethyl, fluorine, chlorine or bromine,

$R_4$ and $R_5$ together also represent an alkylene chain with 4 or 5 chain members, optionally interrupted by O or $NR_6$, and

$R_6$ represents a $C_{1-4}$ alkyl, in the form of acid addition salts and in the form of free bases, characterised in that

a) a compound of formula II



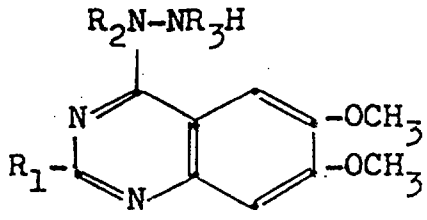
(II)

is reacted with a semicarbazide of formula III

$$HNR_2-NR_3-CO-NR_4R_5 \qquad (III)$$

or

b) a compound of formula IV



(IV)

is reacted with an isocyanate of formula V

$$OCN-R_5 \qquad (V)$$

or

c) a compound of formula IV is reacted with a carbamoyl chloride of formula VI

$$R'_4R'_5-N-COCl \qquad (VI)$$

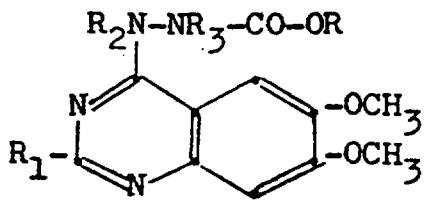
or

d) a compound of formula IV is reacted with a carbaminic acid ester of formula VII

$$R_4R_5-N-COOR \qquad (VII)$$

or

e) a compound of formula VIII



(VIII)

is reacted with a primary or secondary amine of formula IX

$$HNR_4R_5 \qquad (IX)$$

and, if desired, salts obtained according to a) to e) are converted into free bases or salts of other acids, whilst free bases obtained primarily are converted into acid addition salts.