SYNTHESIS AND CARDIOTONIC ACTIVITY OF 6,7-DIMETHOXYQUINAZOLINE DERIVATIVES

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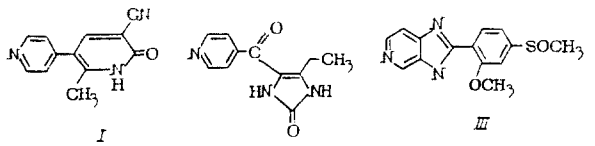
Congestive heart failure is very widespread. More than 50% of 3-4 million patients with congestive heart failure die in one year within the USA [3, 22].

Acute and chronic congestive heart failure, refractoriness to therapy with cardiac glycosides, diuretics, and vasodilators, remains one of the major causes of death in patients with heart diseases [15, 18, 26].

Since reduced myocardial contractility is an important pathophysiologic factor in cardiac failure and cardiac glycosides have a relatively low therapeutic ratio, there is considerable interest in the study of nonglycoside agents with positive inotropic effects [9]. Recent interest has focused on an intensive search for orally active nonglycoside, noncatecholamine cardiotonic agents among various series of different heterocyclic compounds [1, 4, 9-13, 25, 26, 29, 30].

The following pharmacological requirements for new potential nonglycoside, noncatecholamine cardiotonics have been formulated: positive inotropic effects in vitro and on the intact heart, prolonged effects after p.o. administration without the onset of tachyphylaxis, the absence of serious side effects, the absence of direct chronotropic or arrhythmogenic effects, and the presence of a moderate vasodilatory effect [20].

New nonglycoside, noncatecholamine cardiotonics which are active inhibitors of myocardial phosphodiesterase, have been found among a variety of chemical structures, mainly among derivatives of imidazoles and bipyridyls [1, 4, 9, 11, 12, 14, 23-26, 29, 30], and, more recently, among the quinolones and isoquinolones [3, 19, 22]. A number of these substances have been selected for clinical trials as cardiotonics, including milrinone (I) [6, 27], pyroximone (II), [5], isomazol (III) [17, 18, 22], and others [20, 21, 24].



I

II

III

Of these, milrinone (I) is used in medical practice in the USA.

A patent was published in 1984, relating to the positive inotropic effect occurring in parallel with the inhibition of myocardial phosphodiesterase, of derivatives of 6,7-dimethoxy-4-semicarbazidoquinazoline (IC1849) [2]. Subsequent work included a description of the synthesis and study of the cardiotonic activity of the benzene nucleus-substituted 4-alkyl-2-quinazolines and 4-piperidino-6,7-dimethoxyquinazolines, the most active of which after p.o. dosage were 5,6-dimethoxy-4-methyl-2-quinazolinone [7] and 1-butyl-3-[1-(6',7'-dimethoxy-quinazolyl-4') piperidyl-4] urea (buquinazan, IK 14257) [16, 19, 28]. Positive inotropic activity was also found among a number of 4-substituted 6,7-dimethoxyquinazolines described by a group of Indian authors [8].

The availability of 6,7-dimethoxy-2,4-dichloroquinazoline (IV) as a byproduct of the industrial synthesis of the effective hypotensive agent prazocine suggested that it should

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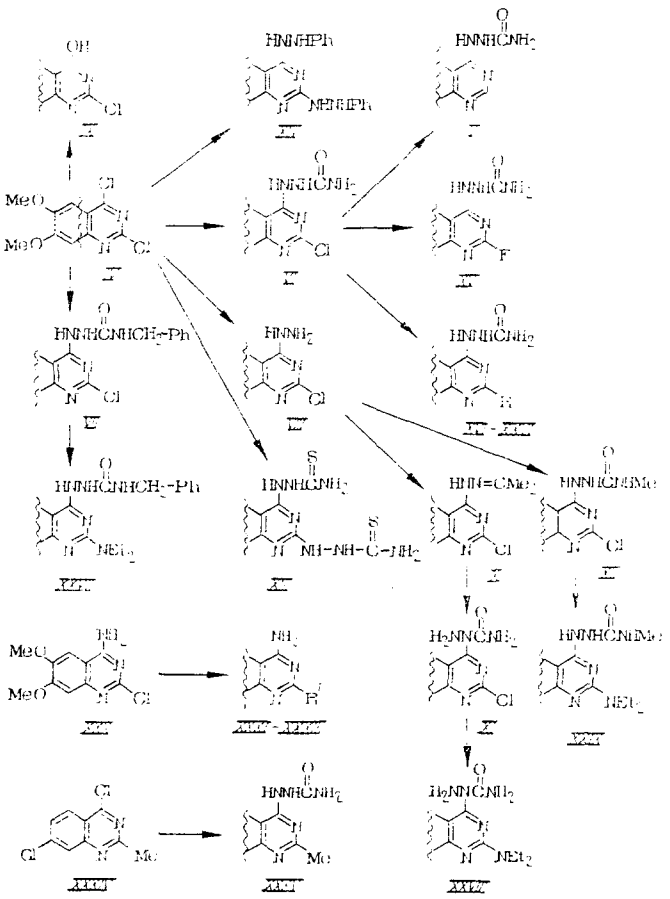

R=$NHNH_2$ (XVI), NEt_2 (XVII), $N(CH_2)_5$ (XVIII), $NHCH_2Ph$ (XIX), $N(CH_2CH_2)_2O$ (XX), $NHCH_2CH_2NH_2$ (XXI), $N(CH_2CH_2)_2NMe$ (XXII), N-(furoyl-2)piperazino XXIII), NHEt (XXIV), NMe_2 (XXV), NBu_2 (XXVI). R'=NHNHC(=S)NH_2 (XXXI), N(Ph)NHC(=S)NH_2 (XXXII), OH (XXXIII).

be used for the synthesis of 6,7-dimethoxy-4-semicarbazidoquinazoline (V) as described in the patent [2], along with new groups of 6,7-dimethoxyquinazoline derivatives, with the aim of testing them for cardiotonic activity.

By using the different reactivities of the chlorine atoms in positions 2 and 4 of compound IV, we utilized its interactions with semicarbazide, 4-benzylsemicarbazide, hydrazine hydrate, and caustic hydroxides to synthesize 2-chloro-6,7-dimethoxy-4-semicarbazidoquinazoline (VI), 2-chloro-6,7-dimethoxy-4-(4'-benzylsemicarbazido)quinazoline (VII), 2-chloro-6,7-dimethoxy-4-hydrazinoquinazoline (VIII), and 2-chloro-6,7-dimethoxy-4-quinazolinone (IX).

The hydrazone (X) was prepared from the hydrazine derivative (VIII) and acetone, and the reaction with NaCNO was used to synthesize 2-chloro-6,7-dimethoxy-4-(2'-semicarbazido) quinazoline (XI). Compound VIII was reacted with MeNCO to produce 2-chloro-6,7-dimethyoxy-4-(4'-methylsemicarbazide) quinazoline (XII).

In the reaction of IV with thiosemicarbazide, the substitution of both chlorine atoms at positions 2 and 4 of the dimethoxyquinazoline ring occurred with equal ease, and the only product obtained, apart from the initial reagent IV, was 6,7-dimethoxy-2,4-dithiosemicarbazidoquinazoline (XIII). This occurred in all cases, even in the presence of insufficient thiosemicarbazide. The reaction of IV with phenylhydrazine resulted in the synthesis of 6,7-dimethoxy-2,4-diphenylhydrazinoquinazoline (XIV).

The reduction of VI in the presence of a palladium catalyst was used to prepare the hydrochloride of 6,7-dimethoxy-4-semicarbazidoquinazoline dihydrate (V). Prolonged (20 h) heating (120°C) of VI with ammonium fluoride in dimethylformamide resulted in the production of the hydrochloride of 2-fluoro-6,7-dimethoxy-4-semicarbazidoquinazoline dihydrate (XV), and the reactions of VI with hydrazine, diethylamine, piperidine, benzylamine, morpholine, ethylenediamine, N-methylpiperazine, N-furoylpiperazine, ethylamine, dimethylamine, and dibutylamine resulted in the synthesis of the respective 6,7-dimethoxy-4-semicarbazido-2-alkylaminoquinazolines (XVI-XXVI). Analogous syntheses starting with compound VII were used to prepare

6,7-dimethoxy-4-(4'-benzylsemicarbazido)-2-diethylaminoquinazoline (XXVII) and, from compounds XI and XII respectively, 6,7-dimethyoxy-4-(2'-semicarbazido)-(XXVIII) and 6,7-dimethoxy-4-(4'-methylsemicarbazido)-(XXIX)-2-diethylaminoquinazolines.

The reaction of 2-chloro-6,7-dimethoxy-4-aminoquinazoline (XXX) with thiosemicarbazide, 1-phenylthiosemicarbazide, and sodium hydroxide resulted in the synthesis of the hydrochlorides of 6,7-dimethoxy-2-thiosemicarbazido-4-aminoquinazoline (XXXI), 6,7-dimethoxy-2-(1'-phenyl-3'-thiosemicarbazido)-4-aminoquinazoline (XXXII), and 6,7-dimethoxy-4-amino-2-quinazoline (XXXII).

The reaction of 4,7-dichloro-2-methylquinazoline (XXXIV) with semicarbazide was used to prepare the hydrochloride of 7-chloro-2-methyl-4-semicarbazidoquinazoline (XXXV).

The melting temperatures, yields, molecular formulae, and the inotropic activities (IC_{50}) and toxicity (LD_{50}) of the compounds prepared are shown in Table 1.

MATERIALS AND METHODS

Infrared spectra of the compounds were taken in Vaseline on a Perkin–Elmer 599 apparatus, and mass spectra were taken on a Varian MAT-112 apparatus at an ionizing electron energy of 70 eV, with direct application of samples to the source.

6,7-Dimethoxy-4-semicarbazidoquinazoline dihydrate hydrochloride (V)

To 1.1 g (3.7 mmol) of VI in 200 ml of ethanol, 0.5 g of $PdCl_2$ in 10 ml of 18% HCl were added, and hydrogen was bubbled through at room temperature at a pressure of 40 cm water, until hydrogenation was complete. After 1 h, the precipitate was collected by filtration, and was washed with hot alcohol (2 × 30 ml). The combined filtrate was evaporated and the residue was recrystallized from ethanol. This reaction produced 0.72 g of V. This material was soluble in alcohols but was poorly soluble in water.

2-Chloro-6,7-dimethoxy-4-semicarbazidoquinazoline (VI)

A mixture of 10 g (40 mmol) of IV and 9 g (120 mmol) of semicarbazide was heated at 50°C in 25 ml of dimethylformamide until it was completely dissolved (5 min) and was then allowed to cool to room temperature. After 24 h, the precipitate was collected by filtration, washed with ethanol, and was recrystallized from anhydrous ethanol. The reaction produced 9.9 g of VI in the form of light yelllow needle-shaped crystals, which were freely soluble in water, alcohols, and dimethylformamide, but poorly soluble in chloroform, and insoluble in ether and heptane. The infra red spectrum was: ν_{max}, cm^{-1}, 1680 (C=O), 1620 (NH_2), 1000, 1250 (C–O–C).

2-Chloro-6,7-dimethoxy-4-(4'-benzylsemicarbazido) quinazoline (VII)

To 4 g (16 mmol) of IV and 3.15 g (16 mmol) of 4-benzylsemicarbazide hydrochloride in 20 ml of dimethylformamide was added 24 ml of Et_3N. After 24 h, 30 ml of water was added, and after 1 h the resulting precipitate was collected by filtration, was washed with 40 ml of ethanol, and was recrystallized from ethanol. This produced 3.1 g of VII in the form of colorless, fibrous crystals, which were freely soluble in alcohols and amines, and poorly soluble in water.

2-Chloro-6,7-dimethoxy-4-drazinoquinazoline (VIII)

To a suspension of 4 g (14 mmol) of IV in 30 ml of ethanol/acetonitrile (1:1) was added, with constant stirring, 1.4 ml (28 mmol) of hydrazine hydrate. These reagents formed a solution in 5 min, and after 20 min, a precipitate formed, which was filtered after 2 h, washed with 20 ml ethanol, an recrystallized from aqueous ethanol. This produced 2.7 g of VIII in the form of colorless crystals. The material was freely soluble in water, alcohols, and dimethylformamide, and insoluble in acetonitrile.

2-Chloro-6,7-dimethoxy-4-quinazolinone (IX)

A mixture of 1 g (3.8 mmol) of IV, 2 g (50 mmol) of NaOH, and 100 ml of 50% isopropanol was boiled for 4 h and acidified and HCl, resulting in the production of 0.74 g IX. This was a light yellow crystalline product, poorly soluble in water and alcohols and more soluble in dimethylformamide.

TABLE 1

Compound	Melting point (decomposition), °C	Yield, %	Molecular formula	Position inotropic activity on isolated guinea pig right atria concn. producing a 50% increase in the contraction amplitude, IC_{50}, M	LD_{50}, mg/kg (i.v., mice)
V	220—2	57,8	$C_{11}H_{13}N_5O_3 \cdot HCl \cdot 2H_2O$	10^{-4}	92,0
VI	170	75	$C_{11}H_{12}ClN_5O_3 \cdot 0,5C_2H_5OH$	**	119,0
VI*	170		$C_{11}H_{12}ClN_5O_3$	**	***
VII	190	51	$C_{18}H_{18}ClN_5O_2$	—	—
VIII	150	62	$C_{10}H_{11}ClN_4O_2 \cdot 0,5H_2O$	**	90,0
IX	247—8	81	$C_{10}H_9ClN_2O_2$	**	***
X	190	68	$C_{13}H_{15}ClN_4O_2 \cdot HCl$	10^{-4}	134,0
XI	180—2	81,7	$C_{11}H_{12}ClN_5O_3 \cdot 0,75H_2O$	**	***
XII	190	68	$C_{12}H_{14}ClN_5O_3$	—	—
XIII	162—3	67	$C_{12}H_{16}N_8O_2S_2 \cdot$ ДМФА	10^{-4}	***
XIV	234—5	91	$C_{22}H_{22}N_6O_2 \cdot HCl$	**	185,0
XV	232—4	52	$C_{11}H_{12}N_5O_3F \cdot HCl \cdot 2H_2O$	**	126,0
XVI	227—8	74	$C_{11}H_{15}N_7O_3 \cdot HCl$	$3 \cdot 10^{-4}$	505,0
XVII	282—4	48	$C_{15}H_{22}N_6O_3 \cdot 0,5H_2O$	10^{-4}	134,0
XVIII	180—2	46	$C_{16}H_{22}N_6O_3 \cdot 0,5H_2O$	**	***
XIX	224—6	60	$C_{14}H_{20}N_6O_3$	**	***
XX	243—4	51	$C_{15}H_{20}N_6O_4$	**	***
XXI	279—81	51	$C_{11}H_{13}N_5O_3 \cdot HCl \cdot 0,75H_2O$	**	180,0
XXII	229—30	74	$C_{16}H_{27}N_7O_3 \cdot HCl \cdot H_2O$	**	268,0
XXIII	237—8	47	$C_{20}H_{23}N_7O_3 \cdot HCl \cdot 0,25H_2O$	**	***
XXIV	305—6	50	$C_{15}H_{18}N_6O_3 \cdot 0,25H_2O$	**	140,0
XXV	252—4	64	$C_{13}H_{18}N_6O_2$	**	***
XXVI	256—8	64	$C_{19}H_{30}NO_3 \cdot HCl \cdot 1,5H_2O$	**	***
XXVII	220—2	70	$C_{22}H_{26}N_6O_3$	**	***
XXVIII	282—4	48	$C_{15}H_{22}N_6O_3 \cdot HCl$	$3,8 \cdot 10^{-5}$	***
XXIX	264—5	45	$C_{16}H_2N_6O_3 \cdot H_2O$	**	
XXIX	264—5	45	$C_{16}H_2N_6O_3 \cdot H_2O$	**	191,0
XXXI	199—200	52	$C_{11}H_{14}N_6O_2S \cdot HCl$	10^{-4}	***
XXXII	237—8	25	$C_{17}H_{18}N_6O_2S \cdot 0,5H_2O$	$8,7 \cdot 10^{-5}$	***
XXXIII	279—80	79	$C_{16}H_{19}N_5O_3 \cdot HCl \cdot 0,5H_2O$	$4,8 \cdot 10^{-5}$	98,0
XXXV	297—9	83	$C_{10}H_{10}ClN_6O \cdot HCl$	$3,4 \cdot 10^{-5}$	352,0
I (milrinone)				$3,8 \cdot 10^{-6}$	

*All compounds were dried at 100°C at a residual pressure of 10-12 mm Hg, and compound VI was additionally dried at 150°C at the same residual pressure for a further 5 h. The results of elemental analyses for carbon, hydrogen, nitrogen, chlorine, sulfur, and direct measurements of water of crystallization corresponded to those calculated for all compounds, the masses of the molecular ions, measured by mass spectroscopy, corresponded to those calculated, and were: VI, 297; VII, 387; XII, 311; XIV, 402, XVII, 334; XXIV, 306; and XXXIII, 221.

**Inactive at concentrations of less than 1 mM.

***Insoluble in water at a concentration of 1%.

2-Chloro-6,7-dimethoxy-4-isopropylidene hydrazinoquinazoline (X)

Compound VIII (3 g, 12 mmol) was heated for 1 h in 40 ml of acetone in the presence of 0.5 g K_2CO_3. The mixture was filtered, evaporated to dryness, and 20 ml of 10% ethanolic HCl was added. The resulting solid was collected by filtration, washed with 30 ml of ether and crystallized from methanol. The reaction yielded 2.7 g of X in the form of light yellow crystals. The substance was freely soluble in water but poorly soluble in acetone.

2-Chloro-6,7-dimethoxy-4-(2'-semicarbazido)quinazoline (XI)

Compound X (2.5 g, 7.5 mmol) was dissolved in 40 ml of water, and 3 ml AcOH was added, and the reaction was stirred for 40 min, while a solution of 2 g (30 mmol) of NaCNO in 30 ml of water was added dropwise. After 12 h, the mixture was heated to 50°C for 30 min, and was then cooled. The resulting precipitate was collected by filtration washed with 40 ml of ethanol, and was recrystallized from aqueous ethanol. The yield was 1.9 of XI in the form of colorless crystals. This material was very soluble in dimethylformamide and poorly soluble in alcohols and water. The infrared red spectrum: ν_{max} cm^{-1}: 1680 (C=O), 1620 (NH_2), 1000, 1250 (C–O–C).

2-Chloro-6,7-dimethoxy-4-(4'-methylsemicarbazido)quinazoline (XII)

To a suspension of 3 g (12 mmol) of VIII in 30 ml was added, with mixing, 1.5 ml (19 mmol) of MeNCO. After 4 h, the precipitate was collected by filtration, washed with 40 ml of MeCN, and crystallized from aqueous ethanol. This reaction yielded 2.5 g of XII in the form of colorless fibrous crystals. The substance was freely soluble in water and poorly soluble in alcohols.

6,7-Dimethoxy-2,4-dithiosemicarbazidoquinazoline hydrochloride (XIII)

A mixture of 7.2 g (27.8 mmol) of IV, 21.3 g (234 mmol) of thiosemicarbazide, and 50 ml of dimethylformamide was agitated for 16 h at 25°C, after which 500 ml of water was added and, after 20 h, a precipitate of 8.22 g of XIII was collected by filtration. The material was a yellow powder, poorly soluble in water and alcohols, but more soluble in hot dimethylformamide.

6,7-Dimethoxy-2,4-di(2'-phenylhydrazino)quinazoline (XIV)

A mixture of 4.6 g (17.7 mmol) of IV, 5 g (46.2 mmol) of phenylhydrazine, 50 ml of MeCN, and 50 ml of absolute ethanol was boiled for 3 h. A precipitate of 6.07 g of XIV was collected by filtration; this was a colorless powder, poorly soluble in alcohols, MeCN, and chloroform, but soluble in water.

2-Fluoro-6,7-dimethoxy-4-semicarbazidoquinazoline dihydrate hydrochloride (XV)

A mixture of 3 g (10 mmol) of VI and 2 g (54 mmol) of ammonium fluoride in 40 ml of dimethylformamide was heated at 120°C for 10 h, was cooled, and the resulting precipitate was collected by filtration, and was washed with 30 ml of methanol, and was recrystallized from aqueous ethanol. The yield was 1.83 g of XV in the form of yellow crystals. The substance was freely soluble in water, but poorly soluble in alcohols.

6,7-Dimethoxy-4-semicarbazido-2-hydrazinoquinazoline hydrochloride (XVI)

A mixture of 1.37 g (4.6 mmol) of VI, 0.53 g (10.6 mmol) of hydrazine hydrate, 4 ml of MeCN, and 10 ml of absolute ethanol was boiled for 6 h. A precipitate of a yellow powder of XVI was collected by filtration; this was poorly soluble in alcohols, AcOH, and dimethylformamide, but was soluble in water.

6,7-Dimethoxy-4-semicarbazido-2,4-diethylaminoquinazoline semihydrate (XVII)

Compound VI (2 g, 7 mmol) and 6 ml (60 mmol) of Et_2NH were boiled for 14 h in 25 ml of ethanol. The resulting solution was evaporated. The residue was boiled in 25 ml of equal volumes of ethanol and MeCN, filtered, and recrystallized from aqueous ethanol. The yield was 1.12 g of XVII, in the form of greenish crystals. The substance was freely soluble in water and amines, and was poorly soluble in alcohols.

Similar reactions were used to prepare compounds XVIII-XXIII.

6,7-Dimethoxy-4-semicarbazido-2-ethylaminoquinazoline (XXIV)

Et_2NH was passed through a solution of 2 g (4 mmol) of VI in 40 ml of anhydrous ethanol at 78°C. After 30 min, the precipitate was collected by filtration and was washed with 20 ml of ethanol and was recrystallized from aqueous ethanol. This yielded 1.02 g of XXIV, in the form of colorless crystals. The substance was freely soluble in water and amines, and was poorly soluble in alcohols.

A similar reaction was used for the preparation of compound XXV.

6,7-Dimethoxy-4-semicarbazido-2-dibutylaminoquinazoline sesquihydrate hydrochloride (XXVI)

A mixture of 2 g (7 mmol) of VI, 4 ml (26 mmol) of Bu_2NH, and 0.2 g of NaBr was boiled for 12 h in 20 ml of ethanol. The reaction was cooled, and the precipitate was collected by filtration, and the filtrate was evaporated in vacuo. Ethanolic HCl (10%, 10 ml) was added, and after 30 min, the precipitate was collected by filtration and recrystallized from aqueous ethanol. The yield was 1.93 g of XXVI in the form of colorless crystals. The substance was freely soluble in alcohols and amines, and poorly soluble in water.

6,7-Dimethoxy-4-(4'-benzylsemicarbazido)-2-diethylaminoquinazoline (XXVII)

Compound VII (2 g, 5 mmol) and 10 ml (100 mmol) of Et_2NH in 30 ml of ethanol was boiled for 20 h. The mixture was evaporated, and the residue was boiled in 30 ml of ethanol/MeCN (1:2), filtered, and recrystallized from ethanol. The yield was 1.62 g of XXVII, in the form of colorless crystals. The substance was insoluble in water, and poorly soluble in alcohols.

Similar reactions were used for the preparation of compounds XXVIII and XXIX.

6,7-Dimethoxy-2-thiosemicarbazido-4-aminoquinazoline hydrochloride (XXXI)

A mixture of 2.7 g (11.2 mmol) of XXX, 1.5 g (16.5 mmol) of thiosemicarbazide, and 30 ml of dimethylformamide was heated for 4 h at 100°C. Compound XXXI (1.93 g) was recovered by filtration, in the form of a light yellow substance, poorly soluble in water, alcohols, and dimethylformamide.

6,7-Dimethoxy-2-(1^1-phenyl-3^1-thiosemicarbazido)-4-aminoquinazoline (XXXII)

A mixture of 3 g (1.5 mmol) of XXX, 2.7 g (16.1 mmol) of 1-phenyl-3-thiosemicarbazide, and 100 ml of dimethylformamide was boiled for 7 h. The reaction was cooled, and 1.3 g of XXXII was collected by filtration in the form of a yellow powder poorly soluble in alcohols and more soluble in water and dimethylformamide.

6,7-Dimethoxy-4-amino-2-quinazolinone hydrochloride (XXXIII)

A mixture of 0.6 g (2.5 mmol) of XXX, 2 g (50 mmol) of NaOH, and 75 ml of 70% methanol was boiled for 20 h, and the reaction was acidified with HCl, and 0.53 g of XXXIII was collected by filtration in the form of a colorless crystalline product poorly soluble in water and alcohols, but more soluble in dimethylformamide.

7-Chloro-2-methyl-4-semicarbazidoquinazoline hydrochloride (XXXV)

To a solution of 5 g (2.3 mmol) of XXXIV in 50 ml of dimethylformamide was added 7 g (23.3 mmol) of semicarbazide at 18-20°C. The reaction was incubated for 3 days, after which 1 liter of 0.005% NaOH was added, and the precipitate was collected by filtration, washed with water (2 × 20 ml) into a flask, along with 60 ml of dimethylformamide, followed by 9 ml of concentrated HCl, and 210 ml of acetone. The reaction was incubated for 2-3 h at 18-20°C, and then for 16 h at 0-5°C. The precipitate was collected by filtration, and was washed with acetone, and was recrystallized from aqueous methanol. The yield was 5.7 g of XXXV, in the form of a water-soluble colorless powder.

Pharmacological Experiments

The pharmacological activity of the compounds was studied on isolated spontaneously contracting guinea pig (180-200 g) right atria by measuring the increase in the amplitude of atrial contractions. Atria were placed in glass vessels ("baths") of 50 ml (the two-channel apparatus produced by Hugo Sacks Electroniks, FRG) containing Krebs-Hanselite solution, which was oxygenated with carbogen (95% O_2 5% CO_2). The strength and frequency of atrial contractions were measured using an isometric transponder model UC-2 (USA). Substances were added to the perfusate 40-60 min after placing atria in the "bath" and stabilization of contractions; increasing concentrations (from 0.1 μM to 1 mM) were used. After 1, 5, 10, and 15 min after the addition of each concentration of compounds, the maximum increases in the frequency and amplitude of contractions were measured. Cardiotonic activity was measured in terms of the IC_{50} values for the effect on contraction amplitude. The additivities of these compounds were compared with the activity of milrinone. Each compound was used in 3-5 experiments.

Acute toxicity was measured on white mice (17-18 g) by i.v. administration.

Pharmacological studies were carried out using compounds V, VI, VIII-XI, XIII-XXIX, XXXI-XXXIII, and XXXV (a total of 28 compounds).

RESULTS AND DISCUSSION

Compounds VI, VIII, IX, XI, XIV, XV, XIII-XXVII, and XXIX were found to have no effect on atrial contractions. Compounds V, X, XIII, XVI, XVII, XVIII, XXI-XXIII, and XXV had positive inotropic effects at concentrations of 10-1000 μM, though they were less active than milrinone by an average of one order of magnitude (Table 1).

Thus, among a series of 6,7-dimethoxyquinazoline derivatives containing substitution groups in positions 2 and 4, substances with positive inotropic effects were identified, although these effects were only moderate.

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