

SPECIFICATION

Urea Derivatives

This invention relates to urea derivatives and, more particularly to N-[3-(lower)alkylaminopropyl]-N'-(disubstituted)phenylureas, which are useful in the treatment of cardiac arrhythmias, and to processes for preparing, and compositions containing the N-[3-(lower)alkylaminopropyl]-N'-(disubstituted)phenylureas. Heretofore the treatment of arrhythmias has been limited by drug toxicity, undesirable side effects, or variable effectiveness. Accordingly a great need exists for an anti-arrhythmic agent which is efficacious and preferably which is less toxic and which has a lower incidence of undesirable side effects than known anti-arrhythmic agents.

The invention provides novel chemical compounds of general formula (I)



wherein:

Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl, 5-bromo-2-methylphenyl, or 5-chloro-2-methylphenyl; and

X is propyl, isopropyl, n-butyl, or isobutyl; and non-toxic pharmaceutically acceptable acid addition salts thereof.

The compounds of formula (I) wherein X is isopropyl are preferred. Also preferred are those compounds of formula (I) wherein Y is 2,6-dimethylphenyl or 5-chloro-2-methylphenyl.

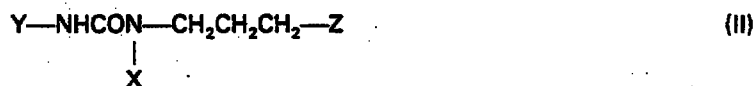
The compounds of formula (I) exhibit cardiac anti-arrhythmic activity as demonstrated in laboratory tests involving a variety of arrhythmic animal models. The compounds are therefore generally useful in treating both atrial and ventricular arrhythmias resulting from various underlying conditions, such as ischemic heart disease, myocardial infarction, congenital cardiac defects, digitalis overdose, myocarditis, or other pathological or toxic processes which may alter the electrical excitability of the heart.

The compound of formula (I) wherein Y is 2,6-dimethylphenyl and X is isopropyl offers significant advantages over known anti-arrhythmic agents because of its low toxicity, longer duration of activity, and low incidence of undesirable side effects. In particular, said compound at therapeutic doses has been found to produce little or no effect on the central nervous system (such as sedation, muscle weakness, or ataxia). Moreover, anti-cholinergic effects were not observed and undesirable cardiac effects (such as depressed cardiac contractility or cardiac output), were minimal at effective dosages.

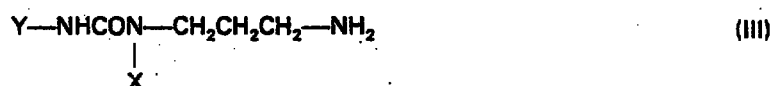
The compound of formula (I) wherein Y is 5-chloro-2-methylphenyl and X is isopropyl also offers particularly significant advantages over known anti-arrhythmic agents because of its high efficacy, particularly long duration of activity, and low incidence of undesirable side-effects.

The compounds of formula (I) can be prepared by conventional synthetic methods. The preferred method is by reaction of an appropriate disubstituted phenyl isocyanate with an N-(lower)-alkyl-1,3-diaminopropane, e.g. in an inert organic solvent, such as dichloromethane. In order to optimise the yield, the reaction can be carried out with an excess of the diaminopropane and at a low temperature. A molar ratio of about 3 to 1 (diamine to isocyanate) is preferred and a temperature of, for example, from -5° to $+5^{\circ}$ C is desirable.

In an alternative method, an appropriate disubstituted phenyl isocyanate may be first reacted with an N-protected-N'-(lower)-alkyl-1,3-diaminopropane, e.g. in an inert solvent, (such as chloroform, dichloromethane, or benzene) to form the protected intermediate of general formula (II):



wherein Y and X have the meanings hereinbefore defined and Z is a protected amino group. The protecting group of the group Z is a conventional protecting group for an amino group and it may then be removed to afford the deprotected intermediate of general formula (III):



If the deprotection step is performed under the influence of heat, the intermediate (III) undergoes an intramolecular aminolysis of the amide *in situ* resulting in substitution of the (lower)alkyl group (X) at the terminal position of the chain. The initial reaction between the isocyanate and the protected diamine may be carried out in an inert solvent, such as chloroform, dichloromethane, or benzene. If the deprotection reaction is carried out at room temperature, the deprotected intermediate III can be isolated, and it can thereafter be converted to the final product by heating the intermediate in a suitable solvent, such as chloroform.

Protecting groups for an amino group are well known in the art. Suitable groups are those which

will prevent undesirable side reactions from occurring at the amino group during the initial reaction and which will be easily removed under mild conditions after the initial reaction.

Methods for making the protected amino compounds and for removing the protecting groups are well-known in the art. Preferred protecting groups are the carbobenzoxy group and the anisylidene group (i.e. preferred Z groups are carbobenzoxyamino or anisylideneamino). The anisylidene group can be removed by treating the protected amine intermediate with hydroxylamine p-toluene-sulfonate in refluxing dioxane or ethyl alcohol. Under such conditions aminolysis takes place *in situ*. The carbobenzoxy group can be removed by treatment with hydrogen bromide in acetic acid at room temperature. The deprotected amine (III) can be isolated and thereafter converted to the final product by mold heating.

In a further method for preparing the compounds of the invention a compound of general formula (IV)



where Y has the meaning given above and W is a halogen atom, preferably chlorine, is reacted with an amine of general formula (V)



where X has the meaning given above. The starting materials of general formula (IV) may be prepared by reacting an appropriate disubstituted phenyl isocyanate with a halopropylamine of general formula (VI)



(where W has the meaning given above) or an acid addition salt thereof.

The compounds of formula (I) can be isolated in the form of the free base or in the form of non-toxic pharmaceutically acceptable acid addition salts prepared by reaction of the free base with a pharmaceutically acceptable organic or inorganic acid. Suitable acids will be apparent to those skilled in the art. Examples of such acids are p-toluene sulfonic (tosyl), hydrochloric or phosphoric. The tosyl and hydrochloric salts are generally preferred.

An effective amount of a compound of formula (I), wherein X and Y are as hereinabove defined, or a non-toxic, pharmaceutically acceptable acid addition salt thereof may be administered orally or parenterally to warm-blooded animals to suppress cardiac arrhythmias in the animals.

The anti-arrhythmic dosage of a compound of formula (I) will vary according to the particular subject being treated, and the severity and nature of the arrhythmia. Therapy should be initiated at a low dosage, the dosage thereafter being increased until the desired anti-arrhythmic effect is obtained. In general, with large warm-blooded animals (about 70 kg. body weight) effective results can be achieved by the oral route at a daily dosage level of, for example, from 0.5 g to 1.5 g (for example, 7 to 20 mg/kg of body weight) given as needed.

In another aspect, the invention provides a pharmaceutical composition comprising: (a) a compound of formula (I), wherein X and Y have the meanings hereinbefore defined, or a non-toxic, pharmaceutically acceptable acid addition salt thereof, and (b) a pharmaceutically acceptable carrier.

The active substances may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. For example, the compounds of formula (I) may be administered orally in solid dosage forms, e.g. solutions or suspensions. The compounds may also be injected parenterally in the form of sterile solutions or suspensions. Solid oral forms may contain conventional excipients for example lactose, sucrose, magnesium stearate and resins. Liquid oral forms may contain various flavouring, colouring, preserving, stabilizing, solubilizing or suspending agents. If desired, additives, such as saline or glucose may be added to make the solutions isotonic. The tosyl salt of the compound of Example 2 is preferred for oral administration and the hydrochloric salt thereof is preferred for administration by injection.

The following Examples 2 to 8 illustrate the invention. Example 1 illustrates the preparation of a starting material. All temperatures are in centigrade.

Example 1

N-Anisylidene-N'-isopropyl-1,3-diaminopropane

A solution of 25 ml of N-isopropyl-1,3-diaminopropane, 20.5 g of p-anisaldehyde and 100 ml of toluene was refluxed in a flask equipped with a water separator. After 4 hours the solution was cooled and extracted with water. After drying over magnesium sulfate, the solution was evaporated to dryness to obtain 34.5 g of N-anisylidene-N'-isopropyl-1,3-diaminopropane. Infrared absorption (film) at 3300 cm^{-1} , 2960 cm^{-1} , 2830 cm^{-1} , 1650 cm^{-1} , 830 cm^{-1} . Nuclear magnetic resonance spectrum ($CDCl_3$): 8.18 δ (S, 1H), 7.70 (d, 2H, J=9 Hz), 6.90 (d, 2H, J=9 Hz), 3.73 (S, 3H), 3.66 (m, 2H), 2.75 (m, 3H), 1.87 (m, 2H), 1.05 (d, 6H), 1.05 (m, 1H exchanges on deuteration).

Example 2**N-[3-(isopropylamino)propyl]-N'-2,6-dimethylphenyl urea****Method A:**

- A solution of 7.4 g of 2,6-dimethylphenylisocyanate and 50 ml of dichloromethane was added to
 5 12 g of N-anisylidene-N'-isopropyl-1,3-diaminopropane dissolved in 100 ml of dichloromethane. The
 solution was refluxed one-half hour, then cooled and extracted with water and with saturated sodium
 carbonate solution. After drying over magnesium sulfate, the dichloromethane was evaporated to
 dryness. The residue was dissolved in 100 ml of ethanol. Eleven grams of hydroxylamine p-
 toluenesulfonate were added and refluxed one-half hour. The solution was evaporated to dryness. The
 10 residue was triturated with hot ether, then dissolved in hot ethanol. Precipitate separated on standing.
 Recrystallization from ethanol afforded N-[3-(isopropylamino)propyl]-N'-2,6-dimethylphenyl urea, 4-
 methylphenyl sulfonate, m.p. 152—155°C. 10

Analysis for: $C_{15}H_{25}N_3O.C_7H_7SO_3$

Calculated:

- 15 C, 60.66; H, 7.64; N, 9.65; S, 7.36 15

Found:

C, 60.61; H, 7.85; N, 9.70; S, 7.07

- IR(KBr) 3380 cm^{-1} , 3280 cm^{-1} , 2650—3100 cm^{-1} , 1670 cm^{-1} , 1550 cm^{-1} ; NMR (DMSO) 8.18—
 8.68 δ (m, 2H, exchange with D_2O), 7.78 (s, 1H, exchanges with D_2O), 6.90—7.65 (m, 7H), 6.48 (m,
 20 1H, exchanges with D_2O), 2.60—3.50 (m, 5H), 2.30 (s, 3H), 2.17 (s, 6H), 1.55—2.05 (m, 2H), 1.19
 (d, 6H). 20

Method B:

- A solution of 73 g of 2,6-dimethylphenylisocyanate and 150 ml of dichloromethane was added
 to a stirred, cooled solution of 150 g of N-isopropyl-1,3-diaminopropane in 400 ml of
 25 dichloromethane. The temperature was kept between -3 and 3°C during the addition. Stirring was
 continued at room temperature for an additional 3 hours. The mixture was extracted with water, then
 with a total of 500 ml of 20% hydrochloric acid (v/v). The acid solution was made basic with saturated
 sodium carbonate solution. The mixture was extracted with dichloromethane. The dichloromethane
 solution was dried over magnesium sulfate, then evaporated to dryness. The residue was treated with
 30 p-toluene-sulfonic acid to obtain the salt. Recrystallization from EtOH afforded N-[3-
 (isopropylamino)propyl]-N'-2,6-dimethylphenylurea, 4-methylphenyl sulfonate, m.p. 152—154°C. 30

Analysis for: $C_{15}H_{25}N_3O.C_7H_7SO_3$:

Calculated:

- 35 C, 60.66; H, 7.64; N, 9.65; S, 7.36

Found:

C, 60.53; H, 7.69; N, 9.45; S, 7.53 35

Hydrochloride, m.p. 162—164°C (Recrystallized from EtOH/Et₂O).Analysis for: $C_{15}H_{25}N_3O.HCl$

Calculated:

- 40 C, 60.08; H, 8.74; N, 14.02; Cl, 11.83 40

Found:

C, 60.02; H, 8.97; N, 14.02; Cl, 11.83

Phosphate m.p. 194—196°C (Recrystallized from EtOH).

Analysis for: $C_{15}H_{25}N_3O.H_3PO_4$

Calculated:

- 45 C, 49.85; H, 7.81; N, 11.63 45

Found:

C, 49.48; H, 7.89; N, 11.54

Example 3

- 50 N-[3-(n-propylamino)propyl]-N'-2,6-dimethylphenylurea 50

- A solution of 14.7 g of 2,6-dimethylphenylisocyanate and 50 ml of dichloromethane was added
 to a stirred, cooled solution of 40 grams of N-n-propyl-1,3-diaminopropane and 350 ml of
 dichloromethane. The temperature was kept between -3 and 0°C during addition. Stirring was
 continued at room temperature for 45 minutes. The solution was extracted with water, then extracted
 55 with a total of 200 ml of 20% hydrochloric acid (v/v). The acid solution was made basic with saturated
 sodium carbonate solution. The basic mixture was extracted with dichloromethane. The 55

dichloromethane solution was dried over magnesium sulfate, then evaporated to dryness. The residue was treated with *p*-toluene-sulfonic acid to obtain the salt. Recrystallization from EtOH/Et₂O afforded N-[3-(*n*-propylamino)propyl]-N'-(2,6-dimethylphenyl)urea, 4-methylphenylsulfonate, m.p. 157—159°C.

Analysis for: C₁₅H₂₅N₃O.C₇H₈SO₃

Calculated:

C, 60.66; H, 7.64; N, 9.65; S, 7.36

Found:

C, 61.01; H, 7.47; N, 9.77; S, 7.09

Example 4

10 N-[3-(isopropylamino)propyl]-N'-(2,5-dimethylphenyl)urea

A solution of 14.7 grams of 2,5-dimethylphenylisocyanate and 50 ml of dichloromethane was added to a stirred, cooled solution of 35 g N-isopropyl-1,3-diaminopropane and 400 ml of dichloromethane. The temperature was kept between -5 and 0°C during addition. Stirring was continued at room temperature for one hour. The solution was extracted with water, then with 200 ml of 15% hydrochloric acid (v/v). The acid extract was made basic with saturated sodium carbonate solution and extracted with dichloromethane. The dichloromethane solution was dried over magnesium sulfate, then evaporated to dryness. The residue was dissolved in ether and saturated with hydrogen chloride. The solid was separated and recrystallized from EtOH/Et₂O to obtain N-[3-(isopropylamino)propyl]-N'-(2,5-dimethylphenyl)urea, hydrochloride, m.p. 152—154°C.

20 Analysis for: C₁₅H₂₅N₃O.HCl

Calculated:

C, 60.80; H, 8.74; N, 14.02; Cl, 11.83

Found:

C, 59.97; H, 8.77; N, 14.03; Cl, 11.74

25 Example 5

N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea

A solution of 16.7 g of 2-methyl-5-chlorophenylisocyanate and 50 ml of dichloromethane was added to a stirred cooled solution of 35 g of N-isopropyl-1,3-diaminopropane and 250 ml of dichloromethane. The temperature was kept at -5 to 0°C during addition. Stirring was continued at room temperature for 20 minutes. The precipitated solid was separated by filtration. The filtrate was extracted with water, then with 200 ml of 15% hydrochloric acid (v/v). The acid extract was made basic with saturated sodium carbonate solution, then extracted with dichloromethane. The dichloromethane solution was dried over magnesium sulfate, then evaporated to dryness. The residue was dissolved in ethanol and saturated with hydrogen chloride. The solution was evaporated to dryness *in vacuo*. The residue was triturated with ether until it solidified. The solid was recrystallized from EtOH/Et₂O to obtain N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea hydrochloride, m.p. 180—183°C.

Analysis for: C₁₄H₂₂N₃ClO.HCl

Calculated:

C, 52.50; H, 7.24; N, 13.12; Cl, 22.14

Found:

C, 52.41; H, 7.08; N, 13.32; Cl, 21.98

Example 6

N-[3-(isopropylamino)propyl]-N'-(5-bromo-2-methylphenyl)urea

(a) A solution of 16.5 grams of 5-bromo-2-methyl aniline and 100 ml of ethylacetate was added with stirring to a solution of 20 grams of phosgene and 300 ml of ethylacetate kept at 5°C. After the addition was completed, phosgene was bubbled through the mixture while refluxing for one half hour. The reaction mixture was purged with nitrogen, then the solvent was removed *in vacuo* to obtain 17 grams of 5-bromo-2-methylphenylisocyanate. This material was dissolved in 150 ml. of chloroform and added cautiously to a solution of 18.2 grams of 3-chloropropylamine hydrochloride, 150 ml. of chloroform, and 20 ml. of triethylamine. The mixture was refluxed for one half hour, then cooled and shaken with water. The precipitated solid was separated by filtration. Recrystallization from ethylacetate afforded N-(3-chloropropyl)-N'-(5-bromo-2-methylphenyl)urea, m.p. 145—148°C.

Analysis for: C₁₁H₁₄BrClN₂O

Calculated:

C, 43.23; H, 4.62; N, 9.16

Found:

C, 43.06; H, 4.55; N, 9.26

(b) Fifteen grams of the above material were combined with 250 ml of chloroform and 50 ml of isopropylamine, then refluxed for 18 hours. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in dichloromethane and shaken with saturated sodium carbonate solution and with water. The dichloromethane solution was extracted with 200 ml. of 20% hydrochloric acid. The acid extract was cooled and made basic with 50% sodium hydroxide solution. The mixture was extracted with dichloromethane. After drying over magnesium sulfate, the dichloromethane was removed *in vacuo*. The residue was dissolved in ethanol and saturated with hydrogen chloride. The solution was evaporated to dryness *in vacuo*. The residue was crystallized by trituration with hot ethylacetate. The solid was recrystallized from ethanol/ether to obtain N-[3-(isopropylamino)propyl]-N'-(5-bromo-2-methylphenyl)urea, hydrochloride, m.p. 180—2°C.

Analysis for: $C_{14}H_{22}N_3BrO.HCl$

Calculated:

C, 46.10; H, 6.35; N, 11.52

Found:

C, 46.11; H, 6.10; N, 11.18.

Example 7

N-[3-(isopropylamino)propyl]-N'-2,6-dimethylphenyl-urea

Triethylamine (56 grams, 0.55 mole) was added to a stirred suspension of 65 grams (0.50 mole) of 3-chloropropylamine hydrochloride and 350 ml of chloroform. The resulting solution was cooled in an ice bath while 73.6 grams (0.50 mole) of 2,6-dimethylphenylisocyanate was added cautiously in portions. After the addition was completed, the solution was refluxed for 20 minutes. The solution was cooled to 15—20°C and 148 grams (2.5 moles) of isopropylamine were added. The solution was refluxed for 20 hours. The solvent and excess isopropylamine were removed *in vacuo*. The residue was dissolved in dichloromethane and extracted with 200 ml of 15% sodium hydroxide solution. The dichloromethane solution was separated and extracted twice with 250 ml of water. The dichloromethane portion was then extracted with a total of 500 ml of hydrochloric acid solution (100 ml conc. HCl and 400 ml of water). The acid extract was cooled and made basic with 50% sodium hydroxide solution. The mixture was extracted with 350 ml of dichloromethane. The dichloromethane solution was washed with water, then dried over magnesium sulphate. The solvent was removed *in vacuo* to obtain 128 grams of waxy solid. This was dissolved in 200 ml of ethanol and 96 grams (0.50 mole) of *p*-toluene-sulphonic acid monohydrate was added and warmed to effect solution. The solvent was evaporated *in vacuo*. The residue was redissolved in ethanol and again evaporated to dryness. The solid residue was slurried with cold ethanol and separated by filtration. The solid was recrystallized from ethanol to obtain 144 grams (66.1%) of N-(2,6-dimethylphenyl)-N'-[3-(1-methylethylamino)propyl]urea, 4-methylbenzenesulphonate, m.p. 152—4°C.

Analysis for: $C_{15}H_{25}N_3O_2S.H$ (435.57)

Calculated:

C, 60.66; H, 7.64; N, 9.65; S, 7.36

Found:

C, 60.61; H, 7.57; N, 9.69; S, 7.67.

Example 8

The suppression of arrhythmias by the compounds of formula (I) can be elicited and demonstrated in the test procedures described below.

In each test, dogs of both sexes are anesthetized by administration of sodium pentobarbital injected I.V. at a dose of 35 mg/kg. Positive pressure artificial respiration with room air is utilized. Blood pressure is recorded from a femoral artery by means of a pressure transducer and oscillograph.

A. Suppression of electrical-stimulated ventricular fibrillations (fibrillatory threshold).

The "fibrillatory threshold" is the voltage at which ventricular fibrillation is produced by an external electrical stimuli delivered to the left ventricle during the repolarization phase of the myocardium. In this test, the anti-arrhythmic activity of a compound is assessed by its ability to increase the fibrillatory threshold in anesthetized dogs.

Ventricular fibrillation is produced in an anesthetized dog by stimulating the left ventricular epicardium for periods of 5 seconds with pulses of 3 msec duration at a frequency of 60 Hz. The stimuli are applied through bipolar platinum electrodes, 3.5 mm apart, embedded in plastic plaque measuring 7×12 mm, which is sutured to the epicardium. The train of stimuli is triggered by the R-wave of the electrocardiogram and applied at increasing intensities (voltages) at 1 min intervals until fibrillation occurs. The animal is defibrillated by a DC countershock and the sequence resumed after 10 min. Test drug is injected I.V. over a period of 5—10 min. Fibrillation threshold is determined before and starting at 10 min after injection of each dose of drug. An increase in threshold of less than +.75 volts is considered inactive; +.75—.99 volts is considered borderline; +1.0—1.24 volts is considered slight; +1.25—1.99 volts is considered moderate; and +2.0 volts or more is considered marked.

When tested by the procedure set forth above, the compounds described in Examples 2, 3, 4, 5,

and 6 produced a moderate to marked increase in fibrillatory threshold at a dose of 10—20 mg/kg. (In this specification, unless indicated otherwise, the compounds were tested in the acid addition salt form obtained in the preparative example for that compound). No material differences in fibrillatory threshold activity were noted between the tosylate and hydrochloride salts of the compound of Example 2. An increase in the P-R interval was observed with the compound of Example 5. The mean ($\pm$ standard deviation) increase in fibrillatory threshold for the compounds of Examples 2—6 at doses of 10 and 20 mg/kg is given in Table I below. The data for the compound of Example 2 is the combined data for the hydrochloride and tosyl salts thereof.

Table I

Compound	Increase in Threshold (Volts)	
	10 mg/kg.	20 mg/kg.
2	1.9 $\pm$.4	2.9 $\pm$.3
3	3.4 $\pm$.1	—
4	2.6 $\pm$ 1.1*	2.5 $\pm$.5*
5	3.5 $\pm$.8	8.8 $\pm$.5
6	1.7 $\pm$.9	6.0 $\pm$.7

* 4 dogs at 10 mg; 2 dogs given additional 10 mg.

B. Suppression of ventricular Arrhythmias Produced by Ouabain.

The I.V. injection of ouabain results in ventricular arrhythmias. In this test, the anti-arrhythmic activity of a compound is assessed by its ability to restore normal sinus rhythm in ouabain-treated, pentobarbital anesthetized dogs. Ouabain is injected I.V. to an anesthetized dog in an initial dose of 50 μ g/kg and then in incremental doses until a ventricular arrhythmia (multiform ventricular beats or ventricular tachycardia) is produced. A total dose of 55 to 60 μ g/kg is usually sufficient to produce the arrhythmia. The test compound is then injected I.V. over approximately 3—5 min., starting 20 min after the injection of ouabain, and the effect on the arrhythmia is observed. Drug injection is terminated when reversion to sinus rhythm is observed. In untreated dogs, the arrhythmia persists greater than 45 minutes.

When tested as set forth above, the compound of Example 2, as the tosyl salt, restored sinus rhythm in four of four dogs at a dose of 7.5 $\pm$ 1.7 mg/kg., and, as the hydrochloride salt, restored sinus rhythm in seven of eight dogs at 6.8 $\pm$ 1.1 mg/kg. In the remaining dog in the latter group, improvement of the arrhythmia was observed, but in view of the absence of a "P" wave in the ECG, a junctional rhythm was assigned. However, this dog received a higher than normal (70 μ g/kg) dose of ouabain.

When tested as described above, compound of Examples 3, 4, 5, and 6 gave the following results:

Table II

Compound	No. of Dogs	Dose (mg/kg)	Results
3	2	7	Restoration of sinus rhythm (2 dogs)
	1	7	Improvement of sinus rhythm (1 dog)
4	3	8	Restoration of sinus rhythm
5	2	10	Restoration of sinus rhythm
6	2	6.8	Restoration of sinus rhythm
	1	7.5	Junctional rhythm (improvement)

C. Suppression of Ventricular Arrhythmias Produced by Coronary Ligation

Ligation of the left anterior descending coronary artery in two stages over a 20 minutes period results in severe ventricular arrhythmias beginning at 5—7 hours and lasting about 48 hours. By the third day, arrhythmias spontaneously subside and normal rhythm is reestablished. The severity of the arrhythmia is greatest within 24 hours following ligation. In this test, the anti-arrhythmic activity of a test compound is assessed by the ability of the compound to restore normal sinus rhythm in the coronary ligated dog. The left anterior descending coronary artery of an anesthetized dog is ligated in two stages at the level of the atrial appendage. The animals recover from anesthesia and the test compound is administered to the conscious dog by I.V. injection or orally (via gastric tube) at 18 to 24 hours after ligation. The test compound is administered until reversion of sinus rhythm occurs or until the intended dose is given.

When tested by I.V. administration about 24 hours post ligation in the procedure set forth above, the compound of Example 2, either as the tosylate salt or the hydrochloride salt, restored complete sinus rhythm in six of six conscious dogs at a dose of 15—20 mg/kg. In two animals, additional compound was administered so that the total dose of >40 mg/kg. Although the animals appeared weaker, no deaths were observed. The compound of Example 3, restored sinus rhythm in two of two dogs at a dose of 10 mg/kg. The compound of Example 4 restored normal sinus rhythm in three of four

dogs when administered in 14—15 mg/kg doses (I.V.). The fourth dog showed no improvement at doses up to 20 mg/kg. The compound of Example 5 restored sinus rhythm in four dogs at doses of 8—20 mg/kg (I.V.). The compound of Example 6 restored sinus rhythm in two of two dogs when administered I.V. according to this procedure at doses of 20 mg/kg.

- 5 When tested in the procedure set forth above by oral administration about 24 hours post ligation, the compound of Example 2, as the tosylate salt, restored sinus rhythm at a dose of 40—50 mg/kg in eight of nine dogs. Although transient weakness appeared in several animals, no prolonged or series side-effects were observed in any of the eight dogs. At a dose of 35 mg/kg in two of three animals a high degree (85—100%) of sinus rhythm was restored with no side-effects observed.
- 10 Oral administration of the compound of Example 2, as the hydrochloride salt, at a single dose of 50 mg/kg restored sinus rhythm but the compound produced general weakness and two out of eight dogs died. Three of three dogs died at a single dose of 75 mg/kg. However, oral administration of the compound of Example 2 as the hydrochloride salt in 2 hourly divided doses totalling 50 mg/kg restored sinus rhythm with no adverse effects. In one dog, transient improvement and brief restoration of sinus rhythm was seen at an initial dose of 35 mg/kg and prolonged restoration of sinus rhythm was seen after an additional dose of 15 mg/kg. In the second dog, an initial dose of 25 mg/kg produced little improvement, but an additional dose of 25 mg/kg produced prolonged restoration of sinus rhythm.
- 15 When tested in the procedure set forth above by oral administration given about 48 hours post ligation, the compound of Example 2, as the tosylate or hydrochloride salt, restored sinus rhythm in four or five dogs at a dose of 15 mg/kg. Significant improvement was observed in one dog at this dose. When administered as either the tosylate or hydrochloride salt at a dose of 25 mg/kg., the compound of Example 2 restored sinus rhythm in six of seven dogs. Marked improvement was observed in one of the dogs at this dose, and restoration of sinus rhythm was observed in the animal after administration of an additional dose of 15 mg/kg.
- 20 When administered orally according to this procedure in doses of 50 mg/kg, the compound of Example 4 restored sinus rhythm in one of three dogs and showed no significant effect in the other two dogs.
- 25 Oral administration of the compound of Example 5 as the tosyl salt at a dose of 50 mg/kg produced less than 50% sinus rhythm. The hydrochloride salt administered orally at the same dose produced sinus rhythm in six of six dogs, and in five of the six dogs this effect was prolonged for from four hours to in excess of six and one-half hours. Oral administration of the compound of Example 5 at a dose of 25 mg/kg produced sinus rhythm in two of three dogs and a marked improvement to predominately sinus rhythm in the third dog.
- 30 When administered orally at a dose of 50 mg/kg, the compound of Example 6 produced normal sinus rhythm in the one dog upon which this procedure was performed. This dosage also caused the dog to wretch.
- 35

Claims

1. A compound of the general formula:



wherein:

- Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl, 5-bromo-2-methylphenyl, or 5-chloro-2-methylphenyl and
X is n-propyl, isopropyl, n-butyl, or isobutyl;
45 or a pharmaceutically acceptable acid addition salt thereof.
2. A compound as claimed in Claim 1 wherein X is isopropyl.
3. A compound as claimed in Claim 1 wherein X is propyl.
4. A compound as claimed in any one of Claims 1 to 3 wherein Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl or 5-chloro-2-methylphenyl.
- 50 5. A compound as claimed in any one of Claims 1 to 3 wherein Y is 5-bromo-2-methylphenyl.
6. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)-urea or a pharmaceutically acceptable acid addition salt thereof.
7. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)-urea, 4-methylphenyl sulphonate.
8. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)urea, hydrochloride.
- 55 9. N-[3-(isopropylamino)propyl]-N'-(2,5-dimethylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.
10. N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.
11. N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea, hydrochloride.
- 60 12. N-[3-(n-propylamino)propyl]-N'-(2,6-dimethylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.
13. N-[3-(isopropylamino)propyl]-N'-(5-bromo-2-methylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.



* C L M S *

dogs when administered in 14—15 mg/kg doses (i.v.). The fourth dog showed no improvement at doses up to 20 mg/kg. The compound of Example 5 restored sinus rhythm in four dogs at doses of 8—20 mg/kg (i.v.). The compound of Example 6 restored sinus rhythm in two of two dogs when administered i.v. according to this procedure at doses of 20 mg/kg.

5 When tested in the procedure set forth above by oral administration about 24 hours post ligation, the compound of Example 2, as the tosylate salt, restored sinus rhythm at a dose of 40—50 mg/kg in eight of nine dogs. Although transient weakness appeared in several animals, no prolonged or series side-effects were observed in any of the eight dogs. At a dose of 35 mg/kg in two of three animals a high degree (85—100%) of sinus rhythm was restored with no side-effects observed.

10 Oral administration of the compound of Example 2, as the hydrochloride salt, at a single dose of 50 mg/kg restored sinus rhythm but the compound produced general weakness and two out of eight dogs died. Three of three dogs died at a single dose of 75 mg/kg. However, oral administration of the compound of Example 2 as the hydrochloride salt in 2 hourly divided doses totalling 50 mg/kg restored sinus rhythm with no adverse effects. In one dog, transient improvement and brief restoration of sinus rhythm was seen at an initial dose of 35 mg/kg and prolonged restoration of sinus rhythm was seen after an additional dose of 15 mg/kg. In the second dog, an initial dose of 25 mg/kg produced little improvement, but an additional dose of 25 mg/kg produced prolonged restoration of sinus rhythm.

20 When tested in the procedure set forth above by oral administration given about 48 hours post ligation, the compound of Example 2, as the tosylate or hydrochloride salt, restored sinus rhythm in four or five dogs at a dose of 15 mg/kg. Significant improvement was observed in one dog at this dose. When administered as either the tosylate or hydrochloride salt at a dose of 25 mg/kg, the compound of Example 2 restored sinus rhythm in six of seven dogs. Marked improvement was observed in one of the dogs at this dose, and restoration of sinus rhythm was observed in the animal after administration of an additional dose of 15 mg/kg.

25 When administered orally according to this procedure in doses of 50 mg/kg, the compound of Example 4 restored sinus rhythm in one of three dogs and showed no significant effect in the other two dogs.

30 Oral administration of the compound of Example 5 as the tosyl salt at a dose of 50 mg/kg produced less than 50% sinus rhythm. The hydrochloride salt administered orally at the same dose produced sinus rhythm in six of six dogs, and in five of the six dogs this effect was prolonged for from four hours to in excess of six and one-half hours. Oral administration of the compound of Example 5 at a dose of 25 mg/kg produced sinus rhythm in two of three dogs and a marked improvement to predominantly sinus rhythm in the third dog.

35 When administered orally at a dose of 50 mg/kg, the compound of Example 6 produced normal sinus rhythm in the one dog upon which this procedure was performed. This dosage also caused the dog to wretch.

Claims

1. A compound of the general formula:

40
$$Y-NHCONH-CH_2CH_2CH_2-NH-X$$
 (I) 40

wherein:

Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl, 5-bromo-2-methylphenyl, or 5-chloro-2-methylphenyl and

X is n-propyl, isopropyl, n-butyl, or isobutyl;

45 or a pharmaceutically acceptable acid addition salt thereof. 45

2. A compound as claimed in Claim 1 wherein X is isopropyl.

3. A compound as claimed in Claim 1 wherein X is propyl.

4. A compound as claimed in any one of Claims 1 to 3 wherein Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl or 5-chloro-2-methylphenyl.

50 5. A compound as claimed in any one of Claims 1 to 3 wherein Y is 5-bromo-2-methylphenyl. 50

6. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)-urea or a pharmaceutically acceptable acid addition salt thereof.

7. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)-urea, 4-methylphenyl sulphonate.

8. N-[3-(isopropylamino)propyl]-N'-(2,6-dimethylphenyl)urea, hydrochloride.

55 9. N-[3-(isopropylamino)propyl]-N'-(2,5-dimethylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof. 55

10. N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.

11. N-[3-(isopropylamino)propyl]-N'-(5-chloro-2-methylphenyl)urea, hydrochloride.

60 12. N-[3-(n-propylamino)propyl]-N'-(2,6-dimethylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof. 60

13. N-[3-(isopropylamino)propyl]-N'-(5-bromo-2-methylphenyl)urea or a pharmaceutically acceptable acid addition salt thereof.



14. A process for preparing a compound claimed in Claim 1 which comprises reacting a disubstituted phenyl isocyanate of general formula



where Y has the meaning given in Claim 1 with an N-alkyl-1,3-diaminopropane of general formula



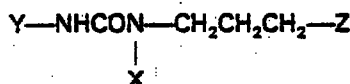
where X has the meaning given in Claim 1 and if desired converting a free base of general formula (I) to a pharmaceutically acceptable acid addition salt thereof.

15. A process as claimed in Claim 14, in which the reaction is carried out with an excess of the N-alkyl-1,3-diaminopropane in an inert organic solvent.

16. A process as claimed in Claim 14 or 15 wherein the reaction is carried out at -5° to $+5^\circ C$.

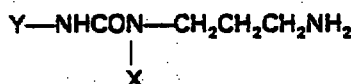
17. A process as claimed in any one of Claims 14 to 16 wherein Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl or 5-chloro-2-methylphenyl.

18. A process for preparing a compound claimed in Claim 1 which comprises removing the protecting group from a protected compound of general formula (II)



(II) 15

(where Y and X are as defined in Claim 1 and Z is a protected amino group) and rearranging the deprotected compound of general formula



(where X and Y are as defined in Claim 1) to a compound as claimed in Claim 1 and if desired,

converting a free base of general formula (I) to a pharmaceutically acceptable acid addition salt thereof.

19. A process as claimed in Claim 18 wherein the removal of the protecting group from the compound of general formula (II) is carried out under the influence of heat such that the deprotected compound of general formula (III) is rearranged *in situ*.

20. A process as claimed in Claim 18 wherein the deprotected compound of general formula (III) is isolated and subsequently rearranged.

21. A process as claimed in any one of Claims 18 to 20 wherein the group Z is amino protected by a carbobenzyoxy or anisylidene group.

22. A process as claimed in any one of Claims 18 to 21 wherein the protected compound of general formula (II) is prepared by reacting a disubstituted phenyl isocyanate of general formula



(where Y is as defined in Claim 1) with a N-protected-N'-alkyl-1,3-diaminopropane of general formula



(where X is as defined in Claim 1 and Z is as defined in Claim 18).

23. A process as claimed in any one of Claims 18 to 22 wherein Y is 2,6-dimethylphenyl, 2,5-dimethylphenyl or 5-chloro-2-methylphenyl.

24. A process for preparing a compound claimed in Claim 1 which comprises reacting a compound of general formula (IV)



(IV)

where Y has the meaning given in Claim 1 and W is a halogen atom, with an amine of general formula (V)



(V)

where X has the meaning given in Claim 1.

25. A process as claimed in Claim 24 wherein the compound of general formula (IV) is prepared by reacting a disubstituted phenyl isocyanate of general formula





19

where Y has the meaning given in Claim 1 with a halopropylamine of general formula



(where W has the meaning given in Claim 24) or an acid addition salt thereof.

26. A process for preparing a compound as claimed in Claim 1 substantially as hereinbefore
5 described with reference to any one of Examples 2A, 2B, 3, 4 and 5. 5
27. A process for preparing a compound as claimed in Claim 1 substantially as hereinbefore
described with reference to Example 6(b) or 7.
28. A compound as claimed in Claim 1 whenever prepared by the process claimed in any one of
Claims 14 to 16, 18 to 22, 24, 25 and 27.
- 10 29. A compound as claimed in Claim 1 whenever prepared by the process claimed in any one of 10
Claims 17, 23 and 26.
30. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to
3, 5, 13 and 28 in association with a pharmaceutically acceptable carrier.
31. A pharmaceutical composition comprising a compound as claimed in any one of Claims 4, 6
15 to 12 and 29 in association with a pharmaceutically acceptable carrier. 15
32. A compound as claimed in any one of Claims 1 to 13, 28 and 29 for use in suppressing
cardiac arrhythmias in warm-blooded animals.