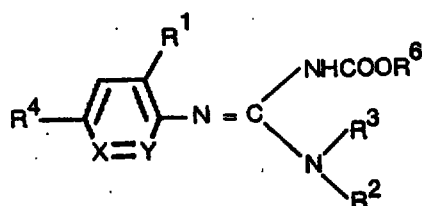


Description

This invention relates to novel guanidine derivatives of the general formula



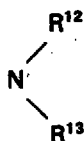
their isomers at the guanidine groups and pharmaceutically acceptable salts of such compounds, wherein

R⁶ is C₁ to 6 alkyl or C₁ to 6 alkyl substituted by C₁ to 6 alkoxy, hydroxy or amino;

one of X and Y is CR and the other is CH or N;

R¹ is hydrogen, halogen, nitro, amino, NHCOR⁸ or NHSO₂R⁸;

R² and R³ are independently selected from hydrogen, N-alkyl-piperidyl (wherein the alkyl group has 1 to 4 carbon atoms), tetrahydropyranyl, morpholinyl, piperidyl and C₁ to C₆ alkyl substituted by one or more substituents selected from OH, SCH₃, OSO₃H, SO₃H, COR⁹, COOR¹⁰, piperazinyl, pyridyl and



with the proviso that R² and R³ cannot both be hydrogen;

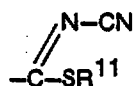
one of R⁴ and R⁵ is selected from hydrogen, C₁ to C₆ alkyl and C₁ to C₆ alkoxy and the other from hydrogen, C₁ to C₆ alkyl and R¹⁴Z wherein R¹⁴ is C₁ to C₆ alkyl or phenyl and Z represents O, S, SO_n or SO₂NR¹⁵ with n being 1, 2 or 3 and R¹⁵ being hydrogen or C₁ to C₆ alkyl; whereby, in the above definitions,

R⁵ is C₁ to C₆ alkyl, C₁ to C₆ alkyl substituted with phenyl or halogen, phenyl or phenyl substituted with C₁ to C₆ alkyl or with halogen;

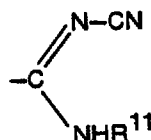
R⁹ is C₁ to C₆ alkyl, C₁ to C₆ acyl or a peptide residue having up to three amino acids;

R¹⁰ is hydrogen or C₁ to C₆ alkyl;

R¹² and R¹³ are independently selected from hydrogen, C₁ to C₆ alkyl,



and



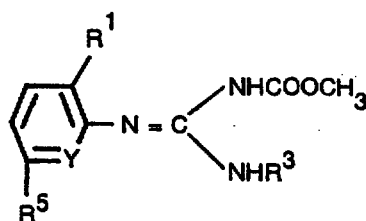
with R¹¹ being C₁ to C₆ alkyl.

The C₁ to C₆ alkyl and alkoxy groups referred to above may be straight or branched chains and include, when the groups have 3 or more C-atoms, cycloalkyl and, when the groups have 4 to 6 C-atoms, also cycloalkylalkyl groups. The tetrahydropyranyl, morpholinyl, piperidyl, piperazinyl, and pyridyl groups include all possible configurations (e.g. 2- 3- and 4-pyridyl). Halogen includes fluorine, chlorine, bromine and iodine. The SO_n-group in the definition of R⁴ and/or R⁵ includes all possible variations, e.g. —OSO₂— and —SO₂O—. Equally the SO₂NR¹⁵— group may be —SO₂NR¹⁵— or —NR¹⁵SO₂—.

The preferred definition of R² is hydrogen and it is equally preferred that only one of R⁴ and R⁵ represents hydrogen and the other is as defined above (except hydrogen). A more important group of compounds is the one wherein R⁴ is hydrogen, X is CR⁶ (with R⁶ being other than hydrogen) and Y is N or CH, preferably CH. The preferred meaning of R¹ is NO₂, NHCOR⁸ or NH₂, and of R³ is a substituted C₁ to C₆ alkyl group wherein the preferred substituents are COOR¹⁰, piperazinyl, pyridyl, NR¹²R¹³, SO₃H and OSO₃H (R¹⁰, R¹² and R¹³ being as defined above). The preferred definition of R⁴ and R⁵ is R¹⁴Z with R¹⁴ being C₁ to C₆ alkyl or phenyl, particularly C₁ to C₆ alkyl and Z being as defined above, but preferably S.

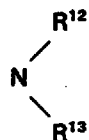
The preferred meaning of R⁶ is CH₃.

The most preferred group of compounds of this invention may be illustrated by the following formula



10 wherein

R¹ is NO₂, NH₂ or NHCOR^a;
R³ is C₁ to C₃ alkyl substituted by



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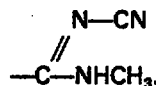
piperazinyl, COOR¹⁰, SO₃H or OSO₃H;

R⁶ is —S—CH₂(CH₂)_mCH₃ (m being 0, 1, 2 or 3, preferably 1);

R^a is C₁ to C₃ alkyl, preferably CH₃;

R¹⁰ is hydrogen or C₁ to C₃ alkyl, preferably hydrogen; and

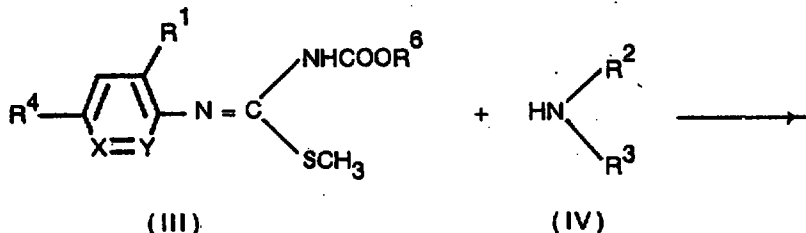
25 R¹² and R¹³ are either both C₁ to C₃ alkyl, preferably ethyl, or one is hydrogen and the other is



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The compounds of this invention may be prepared according to processes generally known in the art for the preparations of similar compounds. Preferably the compounds are obtained according to the reaction illustrated in the following reaction scheme:

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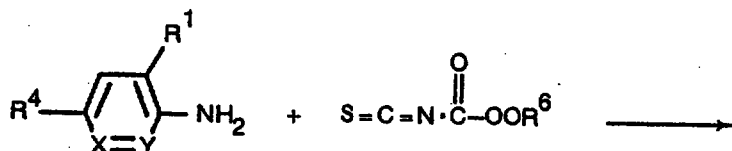
(R¹ to R⁶, X and Y are as defined above).

The reaction is preferably carried out by dissolving the reactants III and IV in an inert solvent, if necessary by heating, and to stir the resulting solution, preferably at ambient temperature, until the reaction is completed.

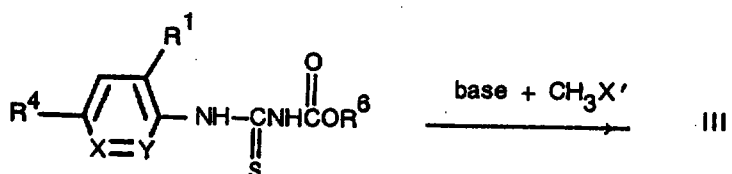
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The starting compounds of formula III are either known or may be obtained by standard reactions well known in the art. The compounds of formula III, for example, may be obtained by following the procedure outlined in Belgian Patent No. 654.306 for the preparation of closely related compounds, i.e.:

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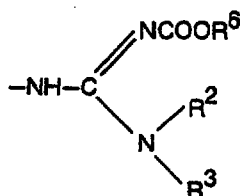
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(R¹, R⁴, R⁸ X and Y are as defined above and X' represents halogen (Cl, Br, or I) or sulfonate).
Included within the scope of this invention are the isomers at the guanidine groups e.g.

(12)



and the salts.

This includes acid addition salts and (metal) salts of those compounds wherein R² and/or R³ represent C₁ to C₈ alkyl substituted by COOR¹⁰ with R¹⁰ being hydrogen, or by OSO₃H or SO₃H. Preferred metal salts are alkali metal salts, in particular sodium salts. The salts are obtained according to standard procedures. Typical acids to be used for forming acid addition salts are hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, propionic, succinic, pamoic, caproic, palmitic and stearic acid.

The following example illustrates the process of this invention.

Example

N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methyl guanidino)ethyl)-N''-(2-nitro-4-propylthiophenyl)guanidine.

Dissolve 6.7 g of N-methoxycarbonyl-N'-(2-nitro-4-propylthiophenyl)-S-methyl-isothioureia and 3.7 g of N'-(2-aminoethyl)-N'-cyano-N''-methyl-guanidine in 50 ml of acetonitrile by heating. Stir the resulting solution for 24 hours at ambient temperature. Remove the solvent by evaporation and chromatograph the residue on 350 g of silica gel, eluting with 1% methanol in methylene chloride to give, after evaporation of the solvent, the title product (m.p. 72—73°C).

By following the process exemplified above, using the appropriate starting compounds, the compounds listed and tabulated below may be prepared:

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-(N-piperazinyl)ethyl)guanidine (m.p. 101—104°C);

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine (m.p. 124°C, dec.);

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethylaminoethyl)guanidine (amber gum);
N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidine (m.p. 116—118°C, dec.);

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-amino-5-propylthiophenyl)guanidine (m.p. 116—119°C, dec.);

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-5-propylthiophenyl)guanidine (m.p. >160°C, dec.);

N-methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidine (m.p. 112—114°C, dec.);

N-methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt (m.p. 195—198°C, dec.);

N-methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-5-propoxyphenyl)guanidine (m.p. 60—63°C);

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-nitro-5-propoxyphenyl)guanidine (m.p. 149—152°C, dec.);

N-methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-4-propylthiophenyl)guanidine (orange viscous oil);

N-methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine;

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-nitro-5-phenylthiophenyl)guanidine (m.p. 181—183°C, dec.);

N-methoxycarbonyl-N'-(2-nitro-4-propyloxyphenyl)-N''-(2-diethylaminoethyl)guanidine (m.p. 91—93°C);

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-4-methyl-5-propoxyphenyl)guanidine (m.p. 225°C, dec.);

N-methoxycarbonyl-N'-(2-pyridylmethyl)-N''-(2-nitro-4-propoxyphenyl)guanidine (m.p. 83—85°C);

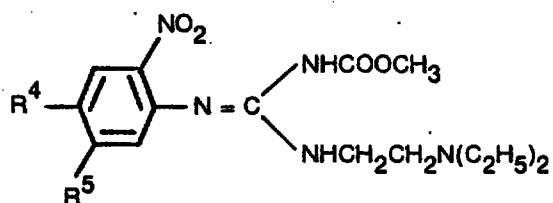
N-methoxycarbonyl-N'-(ethoxycarbonylmethyl)-N''-(2-nitro-5-propoxyphenyl)guanidine (m.p. ≈120°C, dec.);

N-methoxycarbonyl-N'-(2-(1-piperazinyl)ethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine (m.p. 101—104°C);

N-methoxycarbonyl-N'-(2-hydrogensulfate-ethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt (m.p. ≈150°C, dec.); and

N-methoxycarbonyl-N'-(2-sulfonic acid ethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt
(m.p. $\approx 150^\circ\text{C}$, dec.)

TABLE I

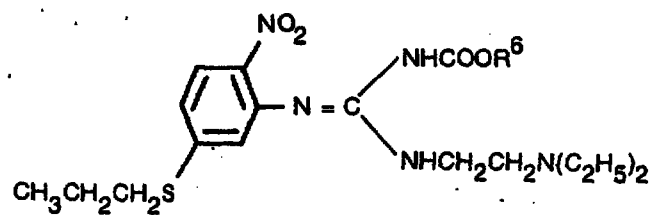


(V)

Compound No.	R ⁴	R ⁵
V A	$-\text{O} \cdot \text{CH}_2\text{CH}_2\text{CH}_3$	H
V B	$-\text{S} \cdot \text{CH}_2\text{CH}_2\text{CH}_3$	H
V C	H	$-\text{O} \cdot \text{CH}_2\text{CH}_2\text{CH}_3$
V D	H	$-\text{SO}_2$ - 
V E	H	$-\text{SO} - \text{CH}_2\text{CH}_2\text{CH}_3$
V F	H	$-\text{SO} -$ 
V G	H	$-\text{SCH}_2\text{CH}_3$
V H	$-\text{O} \cdot \text{C}(\text{CH}_3)_3$	H

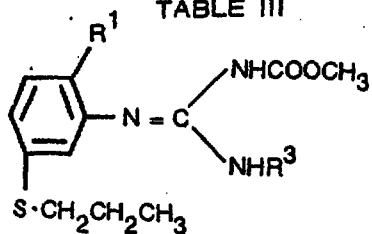
TABLE II

(14)



Compound No.	R ⁶
VI A	C ₂ H ₅
VI B	n-C ₄ H ₉
VI C	-CH ₂ CH(OCH ₃)CH ₃
VI D	-CH ₂ CH(OH)CH ₃
VI E	-CH ₂ CH ₂ NH ₂

TABLE III



(VII)

Compound No.	R ¹	R ³
VII A	Cl	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$
VII B		"
VII C	$\text{ClCH}_2 \cdot \text{CO} \cdot \text{NH}-$	"
VII D		"
VII E		"
VII F		"
VII G	$\text{CH}_3 \cdot \text{SO}_2 \cdot \text{NH}-$	"
VII H	$\text{ClCH}_2 \cdot \text{SO}_2 \cdot \text{NH}-$	"
VII I		"
VII J		"
VII K		"
VII L		"

TABLE III (Continued)

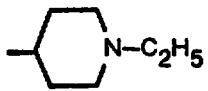
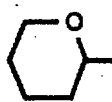
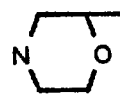
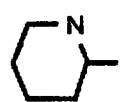
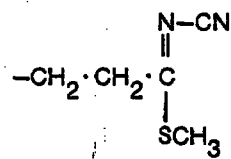
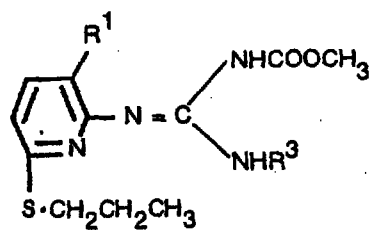
Compound No.	R ¹	R ³
VII M	NO ₂	
VII N	"	
VII O	"	
VII P	"	
VII Q	NH ₂	-CH ₂ CH ₂ OH
VII R	-NHCOCH ₃	-CH ₂ CH ₂ ·S·CH ₃
VII S	NO ₂	-CH ₂ ·CO·C ₂ H ₅
VII T	"	-CH ₂ ·CO·CO·CH ₃
VII U	"	-CH ₂ - (peptide) residue)
VII V	NH ₂	-CH ₂ CH ₂ NH ₂
VII W	NO ₂	
VII X	NO ₂	-CH ₂ ·COOCH ₃

TABLE IV



(VIII)

Compound No.	R^1	R^3
VIII A	NO_2	$-CH_2 \cdot CH_2N(C_2H_5)_2$
VIII B	"	$-CH_2CH_2NH-C \begin{matrix} \nearrow N-CN \\ \searrow NHCH_3 \end{matrix}$
VIII C	"	$-CH_2CH_2-N \begin{matrix} \diagup \\ \diagdown \end{matrix} \begin{matrix} \\ NH \end{matrix}$
VIII D	NH_2	$-CH_2CH_2NH-C \begin{matrix} \nearrow N-CN \\ \searrow NHCH_3 \end{matrix}$
VIII E	$-NH \cdot CO \cdot CH_3$	$-CH_2CH_2NH-C \begin{matrix} \nearrow N-CN \\ \searrow NHCH_3 \end{matrix}$
VIII F	NO_2	$-CH_2CH_2COOH$
VIII G	"	$-CH_2CH_2CH_2COOH$
VIII H	"	$-CH_2COOH$

The compounds of the present invention are useful in combatting helminths, i.e. in treating humans and animals suffering from an infestation of parasitic worms, for example, roundworms, hookworms, whipworms or tapeworms, by administering to the host animal a therapeutic amount of a compound of the present invention.

The compounds of this invention exhibit significant anthelmintic effects when administered to a host (e.g. swine, dogs or ruminants) at doses as low as about one milligram per kilogram of body weight per day in dosing over several days, or at about fifty milligrams per kilogram in a single day dosing, according to techniques well known in the art.

The optimum dose for each species of animal and for each type of parasite can readily be determined by one skilled in the art by using standard techniques such as the Modified McMaster Egg Counting Technique as described by H.B. Whitlock and H. McL. Gordon, J. Council Scientific Industrial Research (Australia) 12, p. 50, 1939 H.B. Whitlock J. Council Scientific Research (Australia) 21, p.177, 1948.

From these, and similar tests, anthelmintic efficacy is assessed by determining the number of eggs in faeces passed on the days following treatment with the compound compared with pre-treatment days. In addition, autopsy of animals after treatment will indicate whether the infection has been eradicated. Based on experimentation, proper dosages for curing various infections can be determined.

The compounds of this invention may be administered in suspensions, capsules, feed additives preparations, tablets, as is well known to those skilled in the human and veterinary medical arts. In addition, the compounds may also be used as injectible anthelmintic preparations. For this purpose, the active ingredient is admixed with suitable sterile carriers such as sterile water and isotonic saline solution.

Suitable clinical formulations containing the compounds of this invention can be administered orally in the form of tablets, capsules and elixirs. The active compound is compounded with inert carriers such as, for example, gums, starches and sugars or it may be incorporated into gelatine capsules or formulated into elixirs which have the advantage of being susceptible to manipulations in flavour by the addition of standard, natural or synthetic flavouring agents.

Particularly useful anthelmintic formulations comprising the compounds of this invention for treatment of helminthiasis are either liquid suspensions ready to use or wettable or water-dispersible powders which are mixed with water prior to use.

A liquid-suspension formulation may contain from 50 to 55% w./v. (kg/liter) of the active compound together with a dispersing agent and stabilizing agent. A typical formulation is as follows:

N-methoxycarbonyl-N'-(2-diethyl-aminoethyl)-N''-(2-nitro-5-propylthiophenyl) guanidine	50 to 55 parts by weight
Dispersing agent	1/2 to 2 parts by weight
Stabilizing agent	1 to 3 parts by weight
Preservative	as required
Water	Sufficient to make 100 volumes.

Suitable dispersing agents are those containing sulphonate groups, for example sodium lignin sulphonate, or the sulphonated phenol or naphthol formaldehyde polymers. Bentonite may be employed as the stabilizing agent, although it is possible to use such protective colloids as carboxymethyl cellulose and sodium alginate. The formulations can be prepared by mixing the active compound and water containing dissolved dispersing agents very vigorously by means of suitable mechanical mixing equipment.

A wettable or water-dispersible powder formulation may contain about 90 to 95% w./w. of the active compound together with a wetting agent and dispersing agent. A diluent such as kaolin can also be added if a concentration below 98% w./w. is required. An anti-foaming agent and, in some cases, a stabilizing agent may be present. A typical formulation is as follows:

N-methoxycarbonyl-N'-(2-diethyl-aminoethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine	90 to 95 parts by weight
Wetting agent	1/2 to 4 parts by weight
Stabilizing agent	0 to 2 parts by weight

Anti-foaming agent

0.01 to 1 part by weight

Water

0 to 5 parts by weight

(9)

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Suitable wetting agents are the non-ionic alkylphenoxyethylene oxide adducts, such as an octylphenol or nonylphenol condensed with ten moles of ethylene oxide, or anionic materials, such as the synthetic aryl alkyl sulphonates, or sodium dibutyl naphthalene sulphonate. In general, about 1% w/w. wetting agent is required. The anti-foaming agent employed may be either a silicone or such materials as ethyl hexanol and octanol; and the stabilizing agent may again be chosen from bentonite or the water-soluble gums. Wettable or water-dispersible powder formulations are prepared by careful and adequate mixing of the active compound with other ingredients with or without the addition of some water using typical powder blending equipment such as a ribbon blender. The powder is stirred into water by the user before application in the field.

15

The following examples show particularly useful formulations:

A. Tablet formulationGrams per 1000 tablets

20	N-Methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine	200.0
	Lactose	90.0
25	Dicalcium phosphate, hydrous	122.5
	Polyvinylpyrrolidone	25.0
	Polyethyleneglycol 1500	7.5
30	Corn Starch	50.0
	Magnesium Stearate	5.0
		500.0

35

Mix the active compound, the lactose and the dicalcium phosphate. Dissolve the polyethyleneglycol 1500 and the polyvinylpyrrolidone in approximately 20 ml of water. Granulate the powder blend with the water solution, adding additional water if necessary, to produce a damp mass. Pass the wet granulation through a 12 mesh screen; spread on trays and air dry at 35°C. Blend the dry granulates with the starch and the magnesium stearate. Compress the 500 mg tablets.

40

B. Capsule formulationGrams per 1000 capsules

45	N-Methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine	200.0
	Lactose	198.0
50	Magnesium Stearate	2.0
		400.0

55

Blend the ingredients and fill into hard gelatine capsules.

C. Elixir formulationper 1000 ml

60	N-Methoxycarbonyl-N'-(2-diethylaminoethyl)-N''-(2-nitro-5-propylthiophenyl)guanidine	40.0 g
	Sodium citrate	10.0 g
65	Sugar	500.0 g

Glycerin	200.0 g
Compound orange spirit	10.0 ml
5 Alcohol	100.0 ml
Amaranth	0.1 ml
Water to total	1000.0 ml

Combine the above ingredients using standard techniques.

15 D. <u>Injectible formulation</u>	<u>mg/ml</u>
N-Methoxycarbonyl-N'-(2-diethylaminoethyl)- N''-(2-nitro-5-propylthiophenyl)guanidine	50.0
Polyethylene Glycol 400	500.0
20 Dimethyl Acetamide	300.0
Benzyl Alcohol	20.0
25 Water for Injection to q.s.	1.0 ml

Combine the above ingredients using standard techniques.

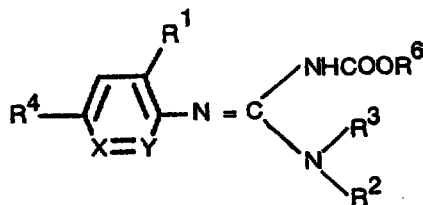
30 E. <u>Injectible formulation</u>	<u>mg/ml</u>
N-Methoxycarbonyl-N'-(2-diethylaminoethyl)- N''-(2-nitro-5-propylthiophenyl)guanidine	100.0
35 Dimethyl Acetamide	300.0
Benzyl Alcohol	20.0
Polyethylene Glycol 400 to q.s.	1.0 ml

Combine the above ingredients using standard techniques.

Similarly may be prepared formulations using other compounds of the present invention, e.g. N-methoxycarbonyl-N'-[2-(N'-cyano-N''-methylguanidino)ethyl]-N''-[2-nitro-5-propylthiophenyl]guanidine.

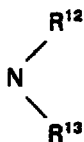
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Compounds of the general formula



their isomers at the guanidine groups and pharmaceutically acceptable salts of such compounds, wherein
 60 R^6 is C_1 to 6 alkyl or C_1 to 6 alkyl substituted by C_1 to 6 alkoxy, hydroxy or amino;
 one of X and Y is CR^5 and the other is CH or N;
 R^1 is hydrogen, halogen, nitro, amino, NHCOR^5 or NHSO_2R^5 ;
 R^2 and R^3 are independently selected from hydrogen, N-alkyl-piperidyl (wherein the alkyl group has 1
 65 substituents selected from OH, SCH_3 , COR^5 , OSO_3H , SO_3H , COOR^{10} , piperazinyl, pyridyl and

(21)



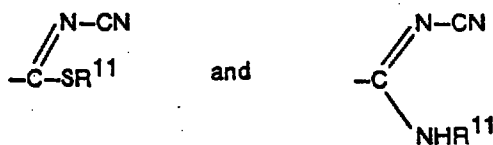
with the proviso that R^2 and R^3 cannot both be hydrogen;

one of R^4 and R^5 is selected from hydrogen, C_1 to C_6 alkyl and C_1 to C_6 alkoxy and the other from hydrogen, C_1 to C_6 alkyl and $R^{14}Z$ wherein R^{14} is C_1 to C_6 alkyl or phenyl and Z represents O, S, SO_n or SO_2NR^{15} with n being 1, 2 or 3 and R^{15} being hydrogen or C_1 to C_6 alkyl; whereby, in the above definitions, R^8 is C_1 to C_6 alkyl, C_1 to C_6 alkyl substituted with phenyl or halogen, phenyl or phenyl substituted with C_1 to C_6 alkyl or with halogen;

R^9 is C_1 to C_6 alkyl, C_1 to C_6 acyl or a peptide residue having up to three amino acids;

R^{10} is hydrogen or C_1 to C_6 alkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_1 to C_6 alkyl,



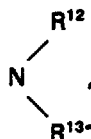
with R^{11} being C_1 to C_6 alkyl.

2. Compounds according to claim 1 wherein R^4 is hydrogen, X is CR^5 and Y is CH or N.

3. Compounds according to claim 2 wherein R^1 is selected from NO_2 , NH_2 and $NHCOR^6$.

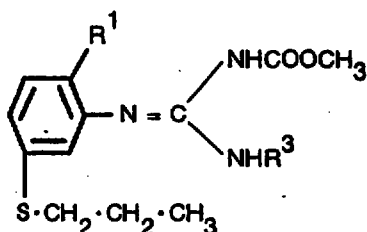
4. Compounds according to claim 3 wherein R^2 is hydrogen, R^3 represents a substituted C_1 to C_6 alkyl group and R^5 is $R^{14}Z$.

5. Compounds according to claim 4 wherein R^3 represents a C_1 to C_6 alkyl group substituted by $COOR^{10}$, piperazinyl, pyridyl,



SO_3H or OSO_3H .

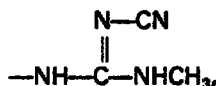
6. Compounds according to claim 5 having the formula



(II),

wherein R^1 is NO_2 , NH_2 or $NHCOCH_3$ and

R^3 is C_1 to C_3 alkyl substituted by a substituent selected from piperazinyl, $COOH$, diethylamino,



SO_3H and OSO_3H .

7. Compounds according to claim 6 being

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-[2-(N-piperazinyl)ethyl]guanidine;

N-methoxycarbonyl-N'-[2(N'-cyano-N''-methylguanidino)ethyl]-N''-[2-nitro-5-propylthiophenyl]guanidine;

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethylaminoethyl)guanidine; N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidine;

N-methoxycarbonyl-N'-[2-(N'-cyano-N''-methylguanidino)ethyl]-N''-(2-amino-5-propylthiophenyl)guanidine;

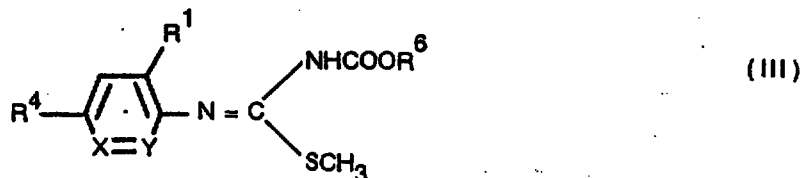
5 N-methoxycarbonyl-N'-[2-(N'-cyano-N''-methylguanidino)ethyl]-N''-[2-acetamido-5-propylthiophenyl]guanidine;

N-methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidine; and

N-methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt.

8. Pharmaceutical compositions comprising as an active ingredient a compound as defined in any one of claims 1 to 7.

9. Process for the preparation of compounds of formula I as defined in claim 1 characterized in that an isothiourea of formula III



20 is reacted with an amine of the formula IV,

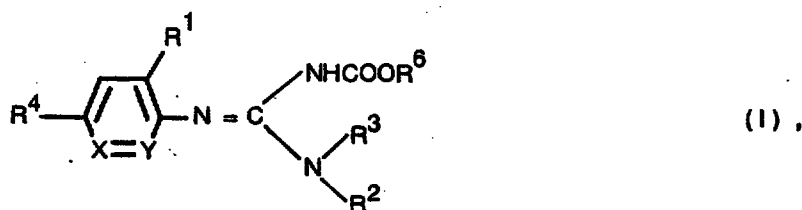


30 whereby in the formulae R¹, R², R³, R⁴, R⁶, X and Y are as defined in claim 1, followed, if desired, by transformation into a salt.

10. Process for preparing pharmaceutical compositions as defined in claim 8, characterized in that a compound as defined in any one of claims 1 to 7, is brought into a form suitable for pharmaceutical application.

Claims for the Contracting State: AT

40 1. Process for the preparation of compounds of the general formula

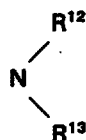


50 their isomers at the guanidine groups and pharmaceutically acceptable salts of such compounds, wherein R⁶ is C₁ to C₆ alkyl or C₁ to C₆ alkyl substituted by C₁ to C₆ alkoxy, hydroxy or amino;

one of X and Y is CR⁵ and the other is CH or N;

R¹ is hydrogen, halogen, nitro, amino, NHCOR⁵ or NHSO₂R⁵;

55 R² and R³ are independently selected from hydrogen, N-alkyl-piperidyl (wherein the alkyl group has 1 to 4 carbon atoms), tetrahydropyranyl, morpholinyl, piperidyl and C₁ to C₆ alkyl substituted by one or more substituents selected from OH, SCH₃, COR⁵, OSO₃H, SO₃H, COOR¹⁰, piperazinyl, pyridyl and



65 with the proviso that R² and R³ cannot both be hydrogen;

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethylaminoethyl)guanidine; N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidine;

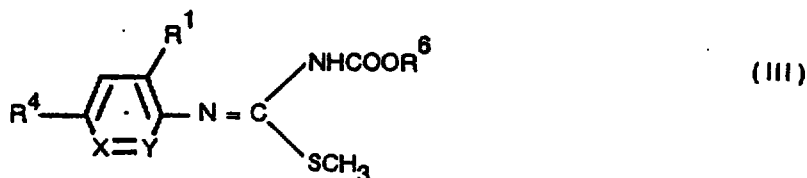
N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-amino-5-propylthiophenyl)guanidine;

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-5-propylthiophenyl)guanidine;

N-methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidine; and N-methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt.

8. Pharmaceutical compositions comprising as an active ingredient a compound as defined in any one of claims 1 to 7.

9. Process for the preparation of compounds of formula I as defined in claim 1 characterized in that an isothiurea of formula III



is reacted with an amine of the formula IV,

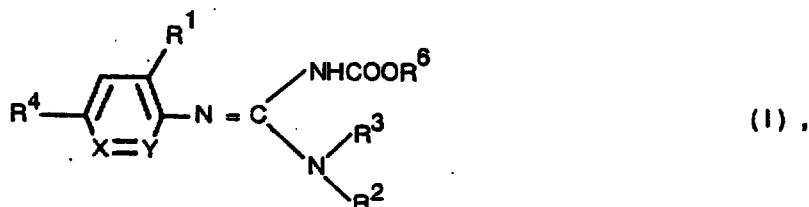


whereby in the formulae R¹, R², R³, R⁴, R⁶, X and Y are as defined in claim 1, followed, if desired, by transformation into a salt.

10. Process for preparing pharmaceutical compositions as defined in claim 8, characterized in that a compound as defined in any one of claims 1 to 7, is brought into a form suitable for pharmaceutical application.

Claims for the Contracting State: AT

1. Process for the preparation of compounds of the general formula

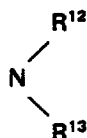


their isomers at the guanidine groups and pharmaceutically acceptable salts of such compounds, wherein R⁶ is C₁ to C₆ alkyl or C₁ to C₆ alkyl substituted by C₁ to C₆ alkoxy, hydroxy or amino;

one of X and Y is CR⁵ and the other is CH or N;

R¹ is hydrogen, halogen, nitro, amino, NHCOR⁶ or NHSO₂R⁶;

R² and R³ are independently selected from hydrogen, N-alkyl-piperidyl (wherein the alkyl group has 1 to 4 carbon atoms), tetrahydropyranyl, morpholinyl, piperidyl and C₁ to C₆ alkyl substituted by one or more substituents selected from OH, SCH₃, COR⁹, OSO₃H, SO₃H, COOR¹⁰, piperazinyl, pyridyl and



with the proviso that R² and R³ cannot both be hydrogen;



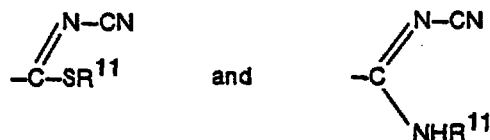
one of R^4 and R^5 is selected from hydrogen, C_1 to C_6 alkyl and C_1 to C_6 alkoxy and the other from hydrogen, C_1 to C_6 alkyl and $R^{14}Z$ wherein R^{14} is C_1 to C_6 alkyl or phenyl and Z represents O, S, SO_n or SO_2NR^{14} with n being 1, 2 or 3 and R^{15} being hydrogen or C_1 to C_6 alkyl; whereby, in the above definitions, R^8 is C_1 to C_6 alkyl, C_1 to C_6 alkyl substituted with phenyl or halogen, phenyl or phenyl substituted with

C_1 to C_6 alkyl or with halogen;

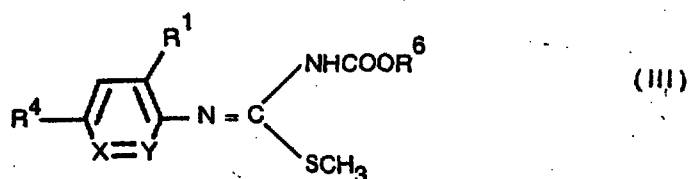
R^9 is C_1 to C_6 alkyl, C_1 to C_6 acyl or a peptide residue having up to three amino acids;

R^{10} is hydrogen or C_1 to C_6 alkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_1 to C_6 alkyl,



with R^{11} being C_1 to C_6 alkyl, characterized in that an isothiourea of formula III



is reacted with an amine of the formula IV,



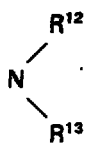
whereby in the formulae R^1 , R^2 , R^3 , R^4 , R^5 , X and Y are as defined in above, followed, if desired, by transformation into a salt.

2. Process according to claim 1, characterized in that compounds wherein R^4 is hydrogen, X is CR^5 and Y is CH or N are prepared.

3. Process according to claim 2, characterized in that compounds wherein R^1 is NO_2 , NH_2 or $NHCOR^6$ are prepared.

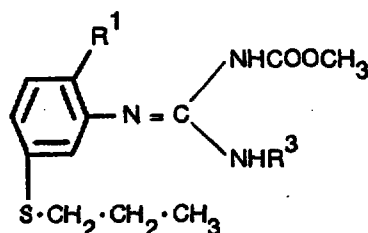
4. Process according to claim 3, characterized in that compounds wherein R^2 is hydrogen, R^3 represents a substituted C_1 to C_6 alkyl group and R^5 is $R^{14}Z$ are prepared.

5. Process according to claim 4, characterized in that compounds wherein R^3 represents a C_1 to C_6 alkyl group substituted by $COOR^{10}$, piperazinyl, pyridyl, SO_3H , OSO_3H ,



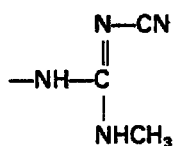
are prepared.

6. Process according to claim 5, characterized in that compounds of the formula



wherein R¹ is NO₂, NH₂ or NHCOCH₃ and

R² is C₁ to C₃ alkyl substituted by a substituent selected from piperazinyl, SO₃H, OSO₃H, COOH, diethylamino and



are prepared.

7. Process according to claim 6, characterized in that the compounds,

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-[2-(N-piperazinyl)ethyl]guanidine;

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-[2-nitro-5-propylthiophenyl]guanidine;

N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethylaminoethyl)guanidine; N-methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidine;

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-amino-5-propylthiophenyl)guanidine;

N-methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-5-propylthiophenyl)guanidine;

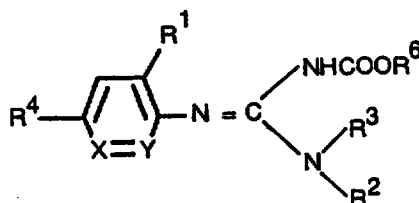
N-methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidine; and

N-methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidine sodium salt are prepared.

8. Process for preparing pharmaceutical compositions, characterized in that a compound as defined in any one of claims 1 to 7 is brought into a form suitable for pharmaceutical administration.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindungen der allgemeinen Formel



(1),

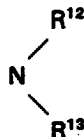
deren Isomere an den Guanidin-Gruppen sowie pharmazeutisch unbedenkliche Salze solcher Verbindungen, worin

R⁶ C₁₋₈-Alkyl oder durch C₁₋₈-Alkoxy, Hydroxy oder Amino substituiertes C₁₋₈-Alkyl ist,

einer der Bausteine X und Y CR⁵ ist und der andere CH oder N ist,

R¹ Wasserstoff, Halogen, Nitro, Amino, NHCOR⁸ oder NHSO₂R⁸ ist,

R² und R³ unabhängig voneinander ausgewählt sind aus Wasserstoff, N-Alkylpiperidyl (worin die Alkyl-Gruppe 1 bis 4 Kohlenstoff-Atome hat), Tetrahydropyranyl, Morpholinyl, Piperidyl und C₁- bis C₈-Alkyl substituiert durch einen oder mehrere Substituenten ausgewählt aus OH, SCH₃, OSO₃H, SO₃H, COR⁹, COOR¹⁰, Piperazinyl, Pyridyl und



ist, mit der Maßgabe, daß R² und R³ nicht beide Wasserstoff sein können,

einer der Substituenten R⁴ und R⁵ ausgewählt ist aus Wasserstoff, C₁- bis C₈-Alkyl und C₁- bis C₈-Alkoxy und der andere ausgewählt ist aus Wasserstoff, C₁- bis C₈-Alkyl und R¹⁴Z, worin R¹⁴ C₁- bis C₈-Alkyl oder Phenyl ist und Z, O, S, SO_n oder SO₂NR¹⁵ bezeichnet, wobei n 1, 2 oder 3 ist und R¹⁵ Wasserstoff oder C₁- bis C₈-Alkyl ist, wobei in den vorstehenden Definitionen



R^8 C₁- bis C₆-Alkyl, durch Phenyl oder Halogen substituiertes C₁- bis C₆-Alkyl, Phenyl oder durch C₁- bis C₆-Alkyl oder Halogen substituiertes Phenyl ist,
 R^9 C₁- bis C₆-Alkyl, C₁-bis C₆-Acyl oder ein Peptid-Rest mit bis zu drei Aminosäuren ist,
 R^{10} Wasserstoff oder C₁- bis C₆-Alkyl ist,
 R^{12} und R^{13} unabhängig voneinander ausgewählt sind aus Wasserstoff, C₁- bis C₆-Alkyl, worin R^{11}



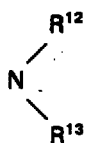
C₁- bis C₆-Alkyl ist.

2. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß R^4 Wasserstoff ist, X CR⁵ ist und Y CH oder N ist.

3. Verbindungen nach Anspruch 2, dadurch gekennzeichnet, daß R^1 ausgewählt ist aus NO₂, NH₂ und NHCOR⁵.

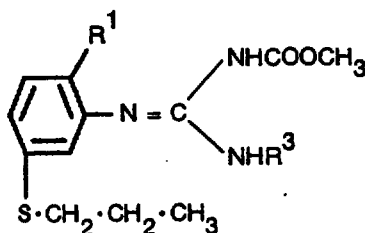
4. Verbindungen nach Anspruch 3, dadurch gekennzeichnet, daß R^2 Wasserstoff ist, R^3 eine substituierte C₁- bis C₆-Alkyl-Gruppe bezeichnet und R^5 R¹⁴Z ist.

5. Verbindungen nach Anspruch 4, dadurch gekennzeichnet, daß R^3 eine C₁- bis C₆-Alkyl-Gruppe bezeichnet, die durch COOR¹⁰, Piperazinyl, Pyridyl,



SO₃H oder OSO₃H substituiert ist.

6. Verbindungen nach Anspruch 5 mit der Formel

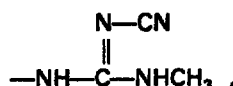


(II) ,

in der

R^1 NO₂, NH₂ oder NHCOCH₃ ist und

R^3 C₁- bis C₃-Alkyl ist, das durch einen Substituenten ausgewählt aus Piperazinyl, COOH, Diethylamino,



SO₃H und OSO₃H substituiert ist.

7. Verbindungen nach Anspruch 6, nämlich

N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-[2-(N-piperazinyl)ethyl]guanidin,

N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-nitro-5-propylthiophenyl)guanidin,

N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethyl-aminoethyl)guanidin,

N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidin,

N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-amino-5-propylthiophenyl)guanidin,

N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-5-propylthiophenyl)guanidin,

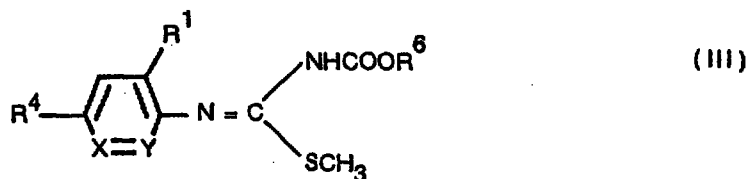
N-Methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidin und

N-Methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidin-Natrium-Salz.

8. Pharmazeutische Zusammensetzungen, enthaltend als Wirkstoff eine Verbindung nach irgendeinem der Ansprüche 1 bis 7.



9. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß ein Isothioharnstoff der Formel III



mit einem Amin der Formel IV

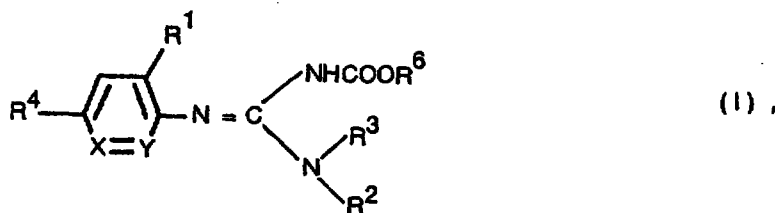


umgesetzt wird, wobei in den Formeln R^1 , R^2 , R^3 , R^4 , R^6 , X und Y die in Anspruch 1 angegebenen Bedeutungen haben, gewünschtenfalls gefolgt von der Überführung in ein Salz.

10. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen nach Anspruch 8, dadurch gekennzeichnet, daß eine Verbindung nach irgendeinem der Ansprüche 1 bis 7 in eine für die pharmazeutische Anwendung geeignete Form gebracht wird.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel



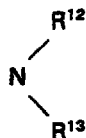
deren Isomerer an den Guanidin-Gruppen sowie pharmazeutisch unbedenklicher Salze solcher Verbindungen, worin

R^6 C_1 - bis C_6 -Alkyl oder durch C_1 - bis C_6 -Alkoxy, Hydroxy oder Amino substituiertes C_1 - bis C_6 -Alkyl ist,

einer der Bausteine X und Y CR^5 ist und der andere CH oder N ist,

R^1 Wasserstoff, Halogen, Nitro, Amino, NHCOR^8 oder NHSO_2R^8 ist,

R^2 und R^3 unabhängig voneinander ausgewählt sind aus Wasserstoff, N-Alkylpiperidyl (worin die Alkyl-Gruppe 1 bis 4 Kohlenstoff-Atome hat), Tetrahydropyranyl, Morpholiny, Piperidyl und C_1 - bis C_6 -Alkyl substituiert durch einen oder mehrere Substituenten ausgewählt aus OH, SCH_3 , OSO_3H , SO_3H , COR^9 , COOR^{10} , Piperaziny, Pyridyl und



ist, mit der Maßgabe, daß R^2 und R^3 nicht beide Wasserstoff sein können,

einer der Substituenten R^4 und R^5 ausgewählt ist aus Wasserstoff, C_1 - bis C_6 -Alkyl und C_1 - bis C_6 -Alkoxy und der andere ausgewählt ist aus Wasserstoff, C_1 - bis C_6 -Alkyl und R^{14}Z , worin R^{14} C_1 - bis C_6 -Alkyl oder Phenyl ist und Z, O, S, SO_n oder $\text{SO}_2\text{NR}^{15}$ bezeichnet, wobei n 1, 2 oder 3 ist und R^{15} Wasserstoff oder C_1 - bis C_6 -Alkyl ist, wobei in den vorstehenden Definitionen

R^8 C_1 - bis C_6 -Alkyl, durch Phenyl oder Halogen substituiertes C_1 - bis C_6 -Alkyl, Phenyl oder durch C_1 - bis C_6 -Alkyl oder Halogen substituiertes Phenyl ist,

R^9 C_1 - bis C_6 -Alkyl, C_1 - bis C_6 -Acyl oder ein Peptid-Rest mit bis zu drei Aminosäuren ist,

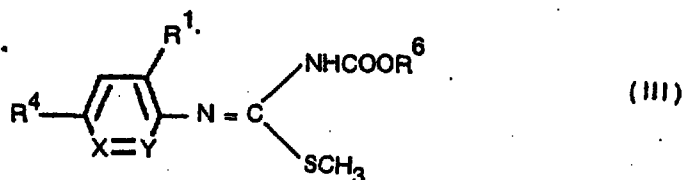


R^{10} Wasserstoff oder C_1 - bis C_6 -Alkyl ist,
 R^{12} und R^{13} unabhängig voneinander ausgewählt sind aus Wasserstoff, C_1 - bis C_6 -Alkyl, worin R^{11}

27



C_1 - bis C_6 -Alkyl ist, dadurch gekennzeichnet, daß ein Isothioharnstoff der Formel (III)



mit einem Amin der Formel (IV)



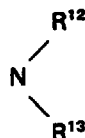
umgesetzt wird, wobei in den Formeln R^1 , R^2 , R^3 , R^4 , R^6 , X und Y die im Vorstehenden angegebenen Bedeutungen haben, gewünschtenfalls gefolgt von der Überführung in ein Salz.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Verbindungen, in denen R^4 Wasserstoff ist, X CR^6 ist und Y CH oder N ist, hergestellt werden.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß Verbindungen, in denen R^1 NO_2 , NH_2 oder $NHCOOR^6$ ist, hergestellt werden.

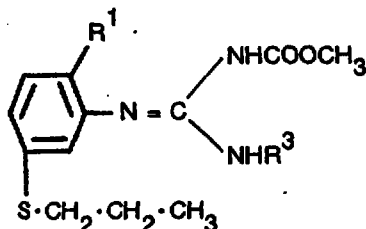
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß Verbindungen, in denen R^2 Wasserstoff ist, R^3 eine substituierte C_1 - bis C_6 -Alkyl-Gruppe bezeichnet und R^6 $R^{14}Z$ ist, hergestellt werden.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß Verbindungen, in denen R^3 eine C_1 - bis C_6 -Alkyl-Gruppe bezeichnet, die durch $COOR^{10}$, Piperazinyl, Pyridyl,



SO_3H oder OSO_3H substituiert ist, hergestellt werden.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß Verbindungen mit der Formel

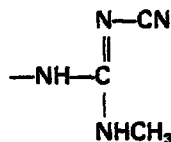


in der

R^1 NO_2 , NH_2 oder $NHCOCH_3$ ist und

R^3 C_1 - bis C_3 -Alkyl ist, das durch einen Substituenten ausgewählt aus Piperazinyl, SO_3H , OSO_3H , $COOH$, Diethylamino und





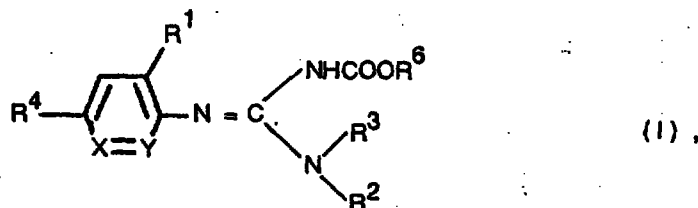
substitué est, hergestellt werden.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß die Verbindungen
 10 N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-(N-piperazinyl)ethyl)guanidin,
 N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-nitro-5-
 propylthiophenyl)guanidin,
 N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-diethyl-aminoethyl)guanidin,
 N-Methoxycarbonyl-N'-(2-nitro-5-propylthiophenyl)-N''-(2-carboxyethyl)guanidin,
 15 N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-amino-5-
 propylthiophenyl)guanidin,
 N-Methoxycarbonyl-N'-(2-(N'-cyano-N''-methylguanidino)ethyl)-N''-(2-acetamido-5-propyl-
 thiophenyl)guanidin,
 N-Methoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophenyl)guanidin und
 20 N-Methoxycarbonyl-N'-carboxymethyl-N''-(2-nitro-5-propylthiophenyl)guanidin-Natrium-Salz
 hergestellt werden.

8. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen, dadurch gekennzeichnet, daß
 eine Verbindung nach irgendeinem der Ansprüche 1 bis 7 in eine für die pharmazeutische Verabreichung
 25 geeignete Form gebracht wird.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composés caractérisés en ce qu'ils sont représentés par la formule générale

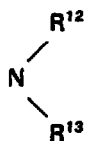


- 40 leurs isomères aux groupes guanidines et des sels pharmaceutiquement acceptables de tels composés, dans laquelle

R⁶ est alkyle C₁ à C₆ ou alkyle C₁ à C₆ substitué par alkoxy C₁ à C₆, hydroxy ou amino;
 un des X et Y est CR⁸ et l'autre est CH ou N;

R¹ est hydrogène, halogène, nitro, amino, NHCOR⁹ ou NHSO₂R⁹;

- 45 R² et R³ sont indépendamment choisis parmi hydrogène, N-alkyl-pipéridyle (dans lequel le groupe
 alkyle a 1 à 4 atomes de carbone), tétrahydropyranyle, morpholinyle, pipéridyle et alkyle C₁ à C₆ substitué
 par un ou plusieurs substituants choisis parmi OH, SCH₃, COR⁹, OSO₃H, SO₃H, COOR¹⁰, pipérazinyle,
 pyridyle et



50 à condition que R² et R³ ne soient pas simultanément l'hydrogène;

un des R⁴ et R⁵ est choisi parmi hydrogène, alkyle C₁ à C₆ et alkoxy C₁ à C₆ et l'autre parmi hydrogène,
 alkyle C₁ à C₆ et R¹⁴Z dans lequel R¹⁴ est alkyle C₁ à C₆ ou phényle et Z représente O, S, SO_n ou SO₂NR¹⁵, n
 60 valant 1, 2 ou 3 et R¹⁵ étant hydrogène ou alkyle C₁ à C₆; dans les définitions ci-dessus;

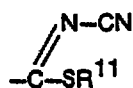
R⁸ est alkyle C₁ à C₆, alkyle C₁ à C₆ substitué par phényle ou halogène, phényle ou phényle substitué par
 alkyle C₁ à C₆ ou par halogène;

R⁹ est alkyle C₁ à C₆, acyle C₁ à C₆ ou un résidu peptide ayant jusqu'à trois amino acides;

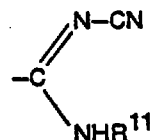
R¹⁰ est hydrogène ou alkyle C₁ à C₆;

- 65 R¹² et R¹³ sont indépendamment choisis parmi hydrogène, alkyle C₁ à C₆,





et



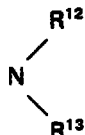
R¹¹ étant alkyle C₁ à C₆.

2. Composés suivant la revendication 1, caractérisés en ce que R⁴ est l'hydrogène, X est CR⁵ et Y est CH ou N.

3. Composés suivant la revendication 2, caractérisés en ce que R¹ est choisi parmi NO₂, NH₂ et NHCOR⁸.

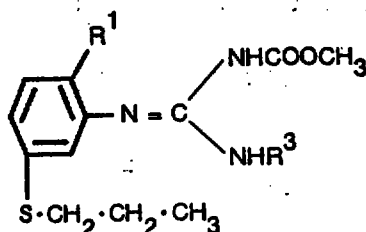
4. Composés suivant la revendication 3, caractérisés en ce que R² est l'hydrogène, R³ représente un groupe alkyle C₁ à C₆ substitué et R⁵ est R¹⁴Z.

5. Composés suivant la revendication 4, caractérisés en ce que R³ représente un groupe alkyle C₁ à C₆ substitué par COOR¹⁰, pipérazinyle, pyridyle,



SO₃H ou OSO₃H.

6. Composés suivant la revendication 5, caractérisés en ce qu'ils sont représentés par la formule

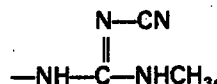


(II)'

dans laquelle

R¹ est NO₂, NH₂ ou NHCOCH₃ et

R³ est alkyle C₁ à C₃ substitué par un substituant choisi parmi pipérazinyle, COOH, diéthylamino,



SO₃H et OSO₃H.

7. Composés suivant la revendication 6, caractérisés en ce qu'ils sont:

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-[2-(N-pipérazinyl)éthyl]guanidine;

N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-[2-nitro-5-propylthiophényl]guanidine;

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-(2-diéthylaminoéthyl)guanidine;

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-(2-carboxyéthyl)guanidine;

N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-(2-amino-5-propylthiophényl)guanidine;

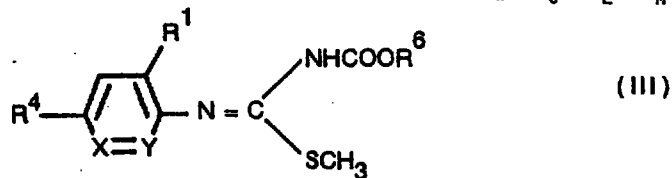
N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-[2-acétamido-5-propylthiophényl]guanidine;

N-méthoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophényl)guanidine; et sel sodique de N-méthoxycarbonyl-N'-carboxyméthyl-N''-(2-nitro-5-propylthiophényl)guanidine.

8. Compositions pharmaceutiques caractérisées en ce qu'elles comprennent comme ingrédient actif un composé comme défini dans n'importe laquelle des revendications 1 à 7.

9. Procédé de préparation de composés de formule I, comme définis dans la revendication 1, caractérisé en ce qu'on fait réagir une isothiourée de formule III





avec une amine de formule IV,

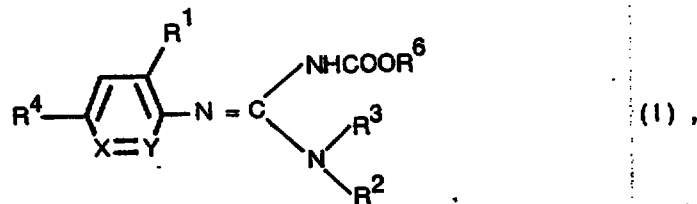


dans lesquelles $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^6, \text{X}$ et Y sont comme définis dans la revendication 1, puis, si on le désire, transforme en un sel.

20 10. Procédé de préparation de compositions pharmaceutiques comme définies dans la revendication 8, caractérisé en ce qu'un composé suivant n'importe laquelle des revendications 1 à 7 est mis sous une forme appropriée pour application pharmaceutique.

25 **Revendications pour l'Etat contractant: AT**

1. Procédé de préparation de composés de formule générale



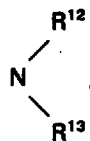
de leurs isomères aux groupes guanidines et des sels pharmaceutiquement acceptables de ces composés, dans laquelle

40 R^6 est alkyle C_1 à C_6 ou alkyle C_1 à C_6 substitué par alkoxy C_1 à C_6 , hydroxy ou amino;

un des X et Y est CR^5 et l'autre est CH ou N ;

R^1 est hydrogène, halogène, nitro, amino, NHCOR^8 ou NHSO_2R^8 ;

45 R^2 et R^3 sont indépendamment choisis parmi hydrogène, N-alkyl-pipéridyle (dans lequel le groupe alkyle a 1 à 4 atomes de carbone), tétrahydropyranyle, morpholinyle, pipéridyle et alkyle C_1 à C_6 substitué par un ou plusieurs substituants choisis parmi OH , SCH_3 , COR^9 , OSO_3H , SO_3H , COOR^{10} , pipérazinyle, pyridyle et



55 à condition que R^2 et R^3 ne soient pas simultanément l'hydrogène;

un des R^4 et R^5 est choisi parmi hydrogène, alkyle C_1 à C_6 et alkoxy C_1 à C_6 et l'autre parmi hydrogène, alkyle C_1 à C_6 et R^{14}Z dans lequel R^{14} est alkyle C_1 à C_6 ou phényle et Z représente O , S , SO_n ou $\text{SO}_2\text{NR}^{15}$, n valant 1, 2 ou 3 et R^{15} étant hydrogène ou alkyle C_1 à C_6 ; dans les définitions ci-dessus;

60 R^8 est alkyle C_1 à C_6 , alkyle C_1 à C_6 substitué par phényle ou halogène, phényle ou phényle substitué par alkyle C_1 à C_6 ou par halogène;

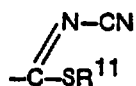
R^9 est alkyle C_1 à C_6 , acyle C_1 à C_6 ou un résidu peptide ayant jusqu'à trois amino-acides;

R^{10} est hydrogène ou alkyle C_1 à C_6 ;

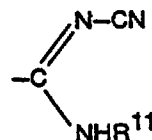
R^{12} et R^{13} sont indépendamment choisis parmi hydrogène, alkyle C_1 à C_6 ,



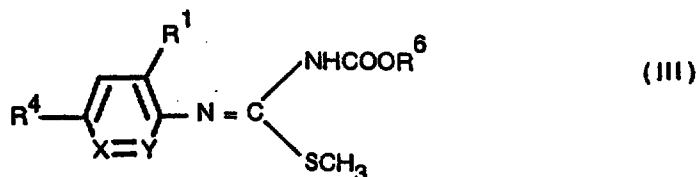
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et



R¹¹ étant alkyle C₁ à C₆, caractérisé en ce qu'on fait réagir une isothiourée de formule III



avec une amine de formule IV,



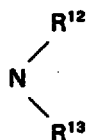
formules dans lesquelles R¹, R², R³, R⁴, R⁶, X et Y sont comme définis ci-dessus, puis, si on le désire, transforme en un sel.

2. Procédé suivant la revendication 1, caractérisé en ce qu'on prépare des composés dans lesquels R⁴ est hydrogène, X est CR⁵ et Y est CH ou N.

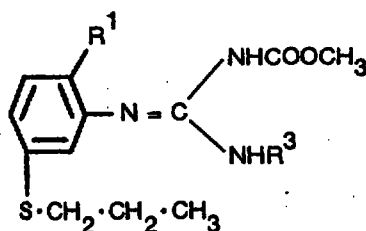
3. Procédé suivant la revendication 2, caractérisé en ce qu'on prépare des composés dans lesquels R¹ est NO₂, NH₂ ou NHCOR⁸.

4. Procédé suivant la revendication 3, caractérisé en ce qu'on prépare des composés dans lesquels R² est hydrogène, R³ représente un groupe alkyle C₁ à C₆ substitué et R⁵ est R¹⁴Z.

5. Procédé suivant la revendication 4, caractérisé en ce qu'on prépare des composés dans lesquels R³ représente un groupe alkyle C₁ à C₆ substitué par COOR¹⁰, pipérazinyle, pyridyle, SO₃H, OSO₃H,



6. Procédé suivant la revendication 5, caractérisé en ce qu'on prépare des composés de formule



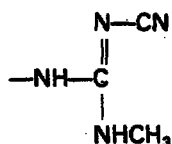
dans laquelle

R¹ est NO₂, NH₂ ou NHCOCH₃ et

R³ est alkyle C₁ à C₃ substitué par un substituant choisi parmi pipérazinyle, SO₃H, OSO₃H, COOH, diéthylamino et



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7. Procédé suivant la revendication 6, caractérisé en ce qu'on prépare les composés suivants:

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-[2-(N-pipérazinyl)éthyl]guanidine;

N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-(2-nitro-5-propylthiophényl)guanidine;

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-(2-diéthylaminoéthyl)guanidine;

N-méthoxycarbonyl-N'-(2-nitro-5-propylthiophényl)-N''-(2-carboxyéthyl)guanidine;

N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-(2-amino-5-propylthiophényl)guanidine;

N-méthoxycarbonyl-N'-(2-(N'-cyano-N''-méthylguanidino)éthyl)-N''-[2-acétamido-5-propylthiophényl]guanidine;

N-méthoxycarbonyl-N'-(3-carboxypropyl)-N''-(2-nitro-5-propylthiophényl)guanidine; et

sel sodique de N-méthoxycarbonyl-N'-carboxyméthyl-N''-(2-nitro-5-propylthiophényl)guanidine.

8. Procédé de préparation de compositions pharmaceutiques caractérisé en ce qu'on composé suivant n'importe laquelle des revendications 1 à 7 est mis sous une forme appropriée pour administration pharmaceutique.