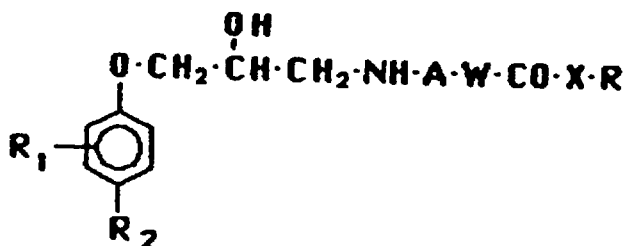


Description

In EP-A-0052072 3-aminopropoxyphenyl derivatives having parasubstituents on the phenyl group and a radical ANHCOXR attached to the amine nitrogen atom are described. The R group is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl or optionally substituted aryl, aralkyl or aralkenyl. In EP-A-0105858 similar compounds are described where the R group is tetrahydropyranyl.

In AU-B-509311 and US-A-4115409 3-aminopropoxyphenyl derivatives in which the R group can contain a heterocyclic group are described. Substituents on the phenyl ring are only ever at the ortho position.

The present invention relates to compounds of Formula I,



wherein

R is furyl, pyranlyl, thienyl, pyrrolyl, indolyl, indolinyl, hydroxyindolinyl, purinyl, hydroxypurinyl, oxindolyl, indazolyl, isoindazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, quinolinyl, quinolinonyl, isoquinolinyl, isoquinolinonyl, quinazolinyl or quinazolinonyl which is separated from the moiety X by a direct bond or an alkylene chain of 1 to 5 carbon atoms or a alkenylene chain of 2 to 5 carbon atoms and is optionally substituted with alkyl of 1 to 4 carbon atoms, or fused with phenyl or optionally mono- or independently di-substituted phenyl with alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number 9 to 53, or any of the above unsaturated ring systems in partly saturated or fully saturated form, provided that R is not tetrahydropyranyl

R₁ is hydrogen, hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, halogen of atomic number 9 to 53, trifluoromethyl, pyrrol-1-yl, cyano, carbamoyl, alkenyl of 2 to 5 carbon atoms, alkenyloxy of 2 to 5 carbon atoms wherein the double bond is at least one carbon removed from the oxygen, alkanoyl of 2 to 5 carbon atoms, nitro, amino, alkanoylamino of 1 to 5 carbon atoms in the alkanoyl moiety, R₂ signifies hydroxy or a group -Z-(CH₂)_n-Y-R₃ wherein R₃ is hydrogen, alkyl or hydroxyalkyl of 1 to 5 carbon atoms, alkenyl of 3 to 7 carbon atoms in which the double bond is at least one carbon removed from Y, cycloalkyl or hydroxy substituted cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl, hydroxy substituted cycloalkylalkyl of 4 to 8 carbon atoms, phenyl or phenylalkyl of 6 to 10 carbon atoms in which the phenyl moiety can either be unsubstituted or

(i) monosubstituted with hydroxy, halogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or carbamoyl,

(ii) independently disubstituted with hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or carbamoyl,

and

Y signifies oxygen or sulfur, and either

Z is an oxygen atom and n is 2 or 3, or

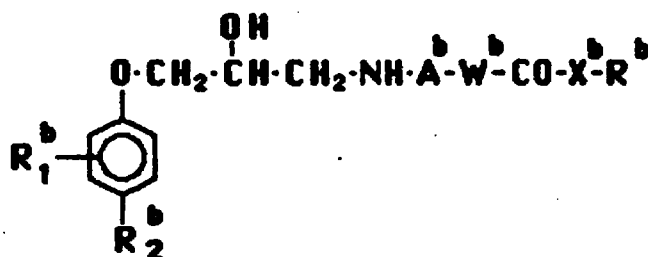
Z is a bond and n is 1, 2 or 3,

A signifies alkylene or branched alkylene of 2 to 5 carbon atoms,

W signifies a bond or imino, and

X signifies a bond or imino, and their physiologically hydrolysable derivatives in which at least one hydroxy group is in esterified form.

A preferred group of compounds of the invention are compounds of Formula Ib,



Ib

wherein,

A^b is preferably ethylene or trimethylene or branched trialkylene on the α -carbon to the nitrogen of the 3-aminopropoxy side chain such as $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2(\text{CH}_2)_2-$.

W^b is preferably imino,

X^b is imino or a bond

R^b is a heterocyclic moiety connected to X by either a direct bond or a methylene moiety and is preferably furyl, thienyl, indolyl, isoindazolyl, 2-oxo-1H-indolyl,

R_1^b is substituted in the 2 position to the 3-aminopropoxy side chain, by hydrogen, hydroxy, cyano, halogen preferably fluoro, carbamoyl, cycloalkyl or alkyl preferably methyl,

R_2^b is hydroxy or a group $\text{Z}-(-\text{CH}_2)_n-\text{Y}-\text{R}_3^b$ in which R_3^b is alkyl or hydroxyalkyl of 1 to 5 carbon atoms, cycloalkylalkyl, hydroxy substituted cycloalkylalkyl of up to 6 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl part, optionally substituted phenyl or phenylalkyl with 1 to 3 carbon atoms in the alkyl portion. Substituents on the benzene ring are preferably hydroxy, alkoxy such as methoxy, alkyl such as methyl or halogen such as fluorine, and

Y is preferably an oxygen atom,

Z is preferably an oxygen atom,

n is preferably 2,

and physiologically hydrolyzable derivatives thereof having at least one hydroxy group in esterified form.

A preferred group are compounds wherein,

A^b , R_1^b , R_2^b , and R^b are as defined above and

W is a bond, and

X is imino,

and physiologically hydrolyzable derivatives thereof having at least one hydroxy group in esterified form.

A further preferred group are compounds wherein,

R_1^b , A^b , R^b and R_2^b are as defined above and,

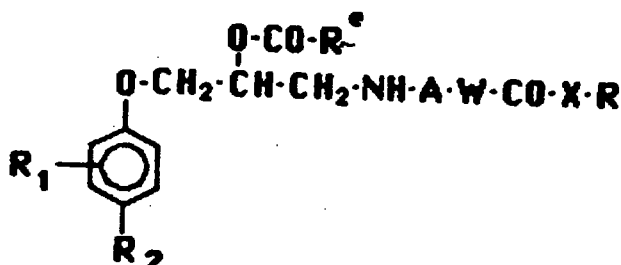
W is imino or a bond, and

X is imino or a bond,

and physiologically hydrolyzable derivatives thereof having at least one hydroxy group in esterified form.

Physiologically hydrolysable esters are derivatives, in which under physiological conditions the esterified hydroxy groups are deesterified to give the corresponding hydroxy compound.

An example of an esterified compound is shown as Formula E,



E

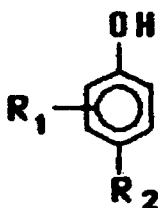
wherein

A, W, X, R, R_1 and R_2 are as defined above and R^e is alkyl of 1 to 12 carbon atoms, cycloalkyl with 3 to 7 carbon atoms, phenyl or phenylalkyl with 7 to 12 carbon atoms.

Preferred are compounds in which the hydroxy group in the 2 position of the 3-aminopropoxy side

chain is in unesterified form.

In accordance with the invention the compounds of the invention may be obtained by a process which includes the step of appropriate 3-amino-2-oxypropylating a corresponding compound of Formula II,



II

wherein R_1 and R_2 are as defined above or a precursor form thereof.

The process step of the invention may be effected in conventional manner for the production of analogous 3-amino-2-oxypropoxyaryl compounds. The choice of the most appropriate variants should, of course, take into account the reactivities of the substituents present.

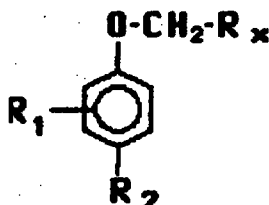
A precursor form of the compound of Formula II is a compound capable of being converted into a compound of Formula II, for example by appropriate etherification, aromatic substitution and/or deprotection. When R_2 is a hydroxy substituent on the phenyl ring it is preferably in protected form.

Thus, the process step of the invention may be effected in more than one stage. For example, a compound of Formula II in protected form may be used or a 3-amino-2-oxypropyl moiety in protected form may be introduced and subsequently after 3-amino-2-oxypropylation has been effected the protecting group present may be split off.

Benzyl, methyl or 2-tetrahydropyranyl, but preferably benzyl are examples of a protecting group on for example a hydroxy substituted ring.

In one form of the process according to the invention the 3-amino-2-oxypropylation is effected in two main process stages.

In the first process stage a group CH_2R_x wherein R_x is a group capable of reacting with a primary amine to give a 2-amino-1-hydroxyethyl group is introduced by O-alkylation in the 1 position into a compound of Formula II to give a corresponding compound of Formula III.



III

wherein R_1 , R_2 and R_x are as defined above.

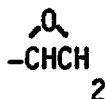
In the second process stage compounds of Formula III is aminated with a corresponding compound of Formula IV,



wherein

A, W, X and R as defined above and where required at least one hydroxy group in a resulting compound of Formula I is appropriately esterified.

The alkylation process stage in the 1 position may be effected in the manner known for the production of analogous ethers. A compound of Formula II is preferably reacted in an ionic form. The amination process stage may be effected in conventional manner for the production of analogous 3-amino-2-hydroxypropoxyaryl compound. For example R_x may be a group of Formula



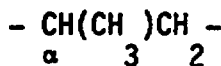
or a derivative of this group for example by a group of Formula CHOHCH_2L wherein L is chlorine, bromine or a group $\text{R}_y\text{SO}_2\text{O}$ wherein R_y is phenyl, tolyl or alkyl. L is especially chlorine. The reaction is preferably effected in ethanol or in an appropriate ether such as dioxane. Optionally an excess of the amine may be used as solvent. Alternatively the reaction may be effected in a fusion melt. Suitable reaction temperature may be from about 20 to about 200°. Conveniently the reflux temperature of the reaction mixture if a solvent is used.

The optional esterification in a resultant compound of Formula I may be affected in a manner known for the production of analogous esters, if necessary using selective conditions when other reactive groups, for example hydroxy or amino are present.

The compounds of the invention may exist in free form, i.e. normally as a base or in salt form. Free forms of the compounds of the invention may be converted into salt forms. For example, acid addition salt forms and vice versa in a conventional manner.

Suitable acids for acid addition salt formation include hydrochloric, malonic, succinic, oxalic and fumaric acids.

In the compounds of the invention the carbon atom in for example the 2 position of the 3-amino-propoxy side chain is asymmetrically substituted and when A is



the alpha carbon atom on the alkylene side chain is also asymmetrically substituted. The compounds may thus exist in racemic form or individual optical isomer forms. The preferred optical isomer has the S-configuration of the asymmetrically substituted carbon atom of the 3-aminopropoxy side chain and when branched on the alkylene side chain the preferred optical isomer has the R-configuration. Individual optical isomer forms may be obtained in conventional manner, for example, by using optically active starting materials or by fractional crystallization of racemate salts using optically active acids.

In so far the preparation of any particular starting materials is not particularly described, this may be effected in conventional manner. In the following examples all temperatures are in degrees centigrade and are uncorrected.

Example 1: N-[2-[3-[2-cyano-4-(2-propoxyethoxy)phenoxy]-2-hydroxypropylamino]-ethyl]-N'-(1H-indol-5-yl)-urea.

4.07 g 2-(2,3-Epoxypropoxy)-5-(2-propoxyethoxy)benzonitrile, 3.2 g N-(2-aminoethyl)-N'-(1H-indol-5-yl)-urea and 200 ml methanol are refluxed together for 5 hours. After removal of the solvent by evaporation the frothy residue is purified by silica gel chromatography under reduced (0.5 bar) pressure using ammonia/methanol/dichloromethane (1:9:90) as eluting phase. After recrystallization from ethylacetate/ether the melting point is 122-124°.

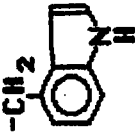
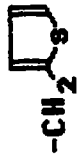
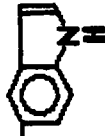
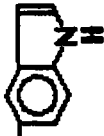
The starting materials are obtained as follows:

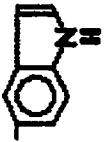
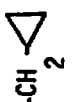
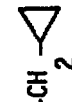
(a) 5 g 1H-indol-5-amine is dissolved in 50 ml pyridine and 6.1 g of chloroacetic acid phenyl ester is added dropwise with vigorous stirring to the mixture held at 0-5°. After 3 hours stirring at room temperature the pyridine is removed by vacuum distillation at 50° and the residue mixed with ice-water and methylenechloride/isopropanol (3:1). After drying of the organic phase with magnesium sulfate and removal of the solvent by evaporation the oily 1H-indol-5-carbamino acid phenyl ester is obtained (used without further purification).

(b) 9.2 g 1H-Indol-5-carbamino acid phenyl ester, 12 ml 1,2-diethylamine and 70 ml dioxane are reacted together with stirring for 2 hours in an oil bath at 100°. After cooling and removal of solvent the residue is mixed with tartaric acid solution and ethylacetate. The aqueous phase is made alkaline with NaOH solution and extracted with dichloromethane/isopropanol (2:1). The extract is dried over magnesium sulfate and evaporated. The crystalline residue is purified over silica gel under reduced (0.5 bar) pressure using conc. ammonia/isopropanol/ethylacetate (5:35:45). Clear fractions are recrystallized from methanol/ether giving N-(2-aminoethyl)-N'-(1H-indol-5-yl) urea (M.P. 156-158°).

The following examples of Formula I are obtained in like manner to Example 1:

Example No.	A	W	X	R	R ₁	R ₃	Y	Z	n	M.P.
2*	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2	118-120°
3**	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2	93-95°
4	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2	126-129°
5	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2	130-132°
6	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN		0	0	2	115-118°
7	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2	120-122°

8	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	Bond		O-CN	Pr	0	0	2	2	b	155-159
9	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	Bond		O-CN	Pr	0	0	2	2	b	100-102
10	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	Bond		O-CN	Pr	0	0	2	2	b	87-89
11	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	Bond		O-CN	Pr	0	0	2	2	b	94-96
12	$-\text{C}(\text{Me})\text{CH} -$ $2 \quad 2$	-NH-	-NH-		O-CN	Pr	0	0	2	2	b	57-62
13	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	-NH-		O-CN	Bu	0	0	2	2	b	119-121
14	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	-NH-		O-CN	$-\text{CH} \text{CH} -$ $2 \quad 2$	0	0	2	2	b	114-116
15	$-\text{CH} \text{CH} -$ $2 \quad 2$	-NH-	-NH-		O-CN	$-\text{CH} \text{CH} -$ $2 \quad 2$	0	0	2	2	b	114-116

16	-CH CH - 2 2	-NH-	-NH-		O-CN	Pr	0	0	2	2	b	144-145 ⁰
17	-CH CH - 2 2	-NH-	-NH-		H	Pr	0	0	2	2	b	119-121 ⁰
18	-CH CH - 2 2	-NH-	-NH-		O-CN	Pr	0	0	2	2	b	162-164 ⁰
19	-CH CH - 2 2	-NH-	-NH-		O-CN		0	0	2	2	b	116-118 ⁰
20	-CH CH - 2 2	-NH-	Bond		O-CN	Pr	0	0	2	2	b	100-102 ⁰
21	-CH CH - 2 2	-NH-	Bond		H		0	0	2	2	b	90-90.5 ⁰
22	-CH CH - 2 2	-NH-	Bond		o-Br		0	0	2	2	b	94.5 ⁰

23	$\begin{array}{c} \text{-CH CH-} \\ 2 \quad 2 \end{array}$	-NH-	Bond		H	$\begin{array}{c} \text{-CH} \\ 2 \end{array}$ 	0	0	2	b	69-70°
24	$\begin{array}{c} \text{-CH CH-} \\ 2 \quad 2 \end{array}$	-NH-	Bond		H	$\begin{array}{c} \text{-CH} \\ 2 \end{array}$ 	0	0	2	ch	192-194°
25 ^{b)}	$\begin{array}{c} \text{CH}_3 \\ \\ \text{-CHCH-} \\ (\text{R,S}) \quad 2 \end{array}$	-NH-	Bond		H	Pr	0	0	2	hf u	43-50°
26	$\begin{array}{c} \text{-CH CH-} \\ 2 \quad 2 \end{array}$	-NH-	Bond		H	Pr	0	0	2	b	71-72°
27	$\begin{array}{c} \text{-CH CH-} \\ 2 \quad 2 \end{array}$	-NH-	Bond		o-Br	Pr	0	0	2	b	77-78°
28	$\begin{array}{c} \text{-CH CH-} \\ 2 \quad 2 \end{array}$	-NH-	Bond		H	Pr	0	0	2	ch	160-162°
29 ^{c)}	$\begin{array}{c} \text{CH}_3 \\ \\ \text{-CH-CH-} \\ (\text{R}) \quad 2 \end{array}$	-NH-	Bond		H	Pr	0	0	2	b	63-65°

	45	40	35	30	25	20	15	10	5
d)	30	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ \text{(R)} \quad 2 \end{array}$	-NH-	Bond		H	2-Me-Pr	0 0 2 2	64-65 ⁰
e)	31	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ \text{(R)} \quad 2 \end{array}$	-NH-	Bond		H	$-\text{CH}_2$	0 0 2 2	83-85 ⁰
	32	$-\text{CH}_2\text{CH}_2-$	-NH-	Bond		H	2-Me-Pr	0 0 2 2	82-84 ⁰
f)	33	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ \text{(R)} \quad 2 \end{array}$	-NH-	Bond		O-F	Pr	0 0 2 2	69-71 ⁰
g)	34	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ \text{(R)} \quad 2 \end{array}$	-NH-	Bond		O-F	2-Me-Pr	0 0 2 2	72-74 ⁰
	35	$-\text{CH}_2\text{CH}_2-$	-NH-	Bond		H	Pr	0 0 2 2	
	36	$-\text{CH}_2\text{CH}_2-$	-NH-	Bond		H	Pr	0 0 2 2	
	37	$-\text{CH}_2\text{CH}_2-$	-NH-	Bond		H	$-\text{CH}_2$	0 0 2 2	

Me = Methyl

b = base

Pr = Propyl

Bu = Butyl

ch = hydrogen chloride salt

M.P. = Melting Point

hfu = hydrogen fumarate salt

- (a) Ortho to the 3-aminopropoxy side chain
- (b) Mixture of 2 diastereomers with the S-configuration on the carbon atom in the 2-position of the 3-amino propoxy side chain; $[\alpha]_D^{20} = -6.64^0$ (c = 1.58/MeOH).
- (c) Mixture of 2 diastereomers with the R configuration on the carbon atom of the group A bond to the nitrogen; $[\alpha]_D^{20} = -8.04^0$ (c = 1.9/MeOH).
- (d) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = 11.43^0$ (c = 1.0/MeOH).
- (e) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.2^0$ (c = 1.22/MeOH).
- (f) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.1^0$ (c = 1.57/MeOH).
- (g) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.30^0$ (c = 0.8/MeOH).
- * The required intermediate 1H-indol-6-acetic acid ethyl ester is obtained from reaction of ethyl iodide with 1H-indol-6-acetic acid in tetrahydrofuran in the presence of 1,8-diazabicyclo [5.4.0] undec-7-an (1,5-5).

** The required intermediate 2,3-dihydro-2-oxo-1H-indol-5-acetic acid methyl ester is obtained from reaction of 5-methoxymethyl-1H-indol-2(3H)-one with hydrochloric acid followed by reaction of the obtained chloride with potassium cyanide/water and saponification of 2,3-dihydro-2-oxo-1H-indol-5-acetonitrile with potassium hydroxide in ethanol and esterification of the obtained 2,3-dihydro-2-oxo-1H-indol-5-acetic acid with methanol in sulfuric acid.

Example 38: 4-[3-[2-Cyano-4-(2-propoxyethoxy)phenoxy]-2-hydroxypropylamino]-N-(1H-indol-5-yl)-butanamide.

3.2 g 2-(2,3-Epoxypropoxy)-5-(2-propoxyethoxy)benzonitrile, 2.5 g of 4-amino-N-(1H-indol-5-yl)-butanamide and 160 ml methanol were refluxed together for 4 hours. After removal of the solvent the residue was purified over silica gel under reduced (0.5 bar) pressure using conc. ammonia/methanol/dichloromethane (1:14:85) as eluting solvent. The clear fractions are recrystallised from methanol/ether giving the title compound (M.P. = 98-100°).

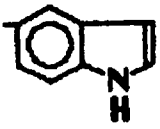
The starting materials are obtained as follows:

(a) Three g of 4-aminobutyric acid is dissolved in 2.33 g of sodium hydroxide and 30 ml water. After addition of 30 ml chloroform the mixture is cooled to 10° and 5.46 g chloroacetic acid benzyl ester is added dropwise with vigorous stirring. After leaving to stand with stirring at room temperature overnight dichloromethane is added and the mixture allowed to partition. The aqueous phase is saturated with sodium chloride and extracted with methylene chloride. After drying over magnesium sulfate the solvent is removed by evaporation in vacuo giving the oily 4-(benzyloxycarbonylamino)butyric acid.

(b) 6.76 g of 4-(Benzyloxy-carbonylamino)butyric acid is dissolved in 70 ml dichloromethane and reacted with 2.94 g dicyclohexylcarbodiimide at room temperature. After 2 hours stirring the precipitate is filtered, washed with 25 ml dichloromethane and reacted with 3.6 g sodium hydrogen carbonate and 3.44 g 5-aminoindole. After 17 hours stirring at room temperature 150 ml water is added and after a half hour vigorous stirring the dichloromethane phase is removed and the aqueous phase re-extracted twice more with dichloromethane which is finally dried over magnesium sulfate. After removal of the solvent the oily residue is purified over silica gel under reduced pressure (0.5 bar) using toluene/ethylacetate (2:1) giving 4-(benzyloxycarbonylamino)-N-(1H-indol-5-yl) butanamide (oil).

(c) 4.56 of 4-(Benzyloxycarbonylamino)-N-(1H-indol-5-yl)butanamide, 1.1 g palladium (10%) on charcoal and 100 ml methanol are added together at room temperature in the presence of hydrogen until about 90% of theoretical hydrogen uptake is obtained (maximum uptake). The suspension is filtered through talc and the solvent evaporated off giving an oily residue of 4-amino-N-(1H-indol-5-yl)butanamide which is recrystallised from methanol/ether (M.P. 124-136°).

The following example is obtained in analogous manner to Example 38.

Example	A	W	X	R	R ^{1*}	R ³	Z	Y	n
39	$-(\text{CH}_2)_2-$ 0	Bond	-NH		O-CN	Pr	0	0	2
M.P. 117-119									

b = base

*o = ortho to 3-aminopropoxy side chain

The compounds of the invention in free form or as their physiologically acceptable salt possess unique pharmacological activity and can be used as therapeutic agents in man.

In particular the compounds possess beta adrenoceptor blocking activity as indicated by standard tests for example, in the spontaneously beating guinea pig atrium (A. Bertolet et al., Postgraduate Medical Journal, 57, Suppl. 1, 9-17, 1981). They inhibit the positive chronotropic isoproterenol effect at bath concentrations from about 10^{-9} to 10^{-8} mol/l.

Thus, in the test above selected compounds have the following potencies expressed as a dose which doubles the concentration of isoproterenol needed to elicit a 50% increase in heart rate (i.e. ID₅₀).

Example No.	Guinea Pig Atrium, Effective Molar Dose, M (ID ₅₀)
1	3.0×10^{-9}
4	2.2×10^{-9}
5	1.2×10^{-9}
6	1.3×10^{-8}
9	2.5×10^{-8}
11	1.2×10^{-8}
14	1×10^{-8}
19	1×10^{-7}
20	5×10^{-8}
29	3×10^{-8}
33	8×10^{-9}
Propranolol	3×10^{-9}
Atenolol	2×10^{-7}
Metoprolol	1.2×10^{-8}

The beta adrenoceptor blocking activity in the heart can also be demonstrated in a whole animal model. For example the inhibition of isoproterenol-induced tachycardia in the pithed rat show in vivo potencies many times higher than expected from their potencies in the guinea pig atrium model and for standard compounds known in the art.

Thus, in the test above, the following compounds exhibit effective beta adrenoceptor blocking activity at doses indicated below:

Example No.	Pithed Rat Effective Dose (ID50) (ug/kg)
1	2
5	2
19	100
23	30
27	5
28	3
29	50
Propranolol	20
Atenolol	30
Betaxolol	10

The compounds are particularly useful as beta adrenoceptor blocking agents and can therefore be used for the prophylaxis and therapy of diseases which are commonly known to respond to blockade of beta adrenoceptors such as those found in the heart. Examples of such diseases are hypertension, angina pectoris, thyrotoxicosis, migraine, glaucoma and for the treatment of disturbances of the heart rhythm such as supraventricular tachycardia.

In addition, the compounds have more marked and wider spread beneficial pharmacological properties than would be expected for compounds having this type of structure. In particular, their activity is more cardioselective than presently known for similar compounds.

This can be demonstrated in vivo in tracheal preparations of the guinea pig which are prepared according to standard procedures in which a portion of the tracheal muscle is allowed to relax under the influence of isoproterenol and in the presence of known concentrations of the compound to be tested. Selected examples are shown below:

Example No.	Guinea Pig Trachea Effective Molar Dose, ID50
1	5×10^{-5}
4	$>1 \times 10^{-4}$
5	4×10^{-5}
6	5×10^{-5}
9	2×10^{-5}
11	4×10^{-6}
14	5×10^{-5}
19	5×10^{-5}
20	6×10^{-5}
29	6×10^{-5}
33	6×10^{-5}
Betaxolol	1×10^{-6}
Atenolol	3×10^{-6}
Propranolol	5×10^{-9}

In these preparations the potency of all examples are much less than in the atrial preparations described above and most have no blocking activity in the tracheal preparation at concentrations of 1×10^{-5} molar and for many compounds much higher concentrations than 1×10^{-5} molar are needed to show blocking activity in the trachea indicating that these compounds have virtually absolute selectivity for the cardiac (atrial) beta adrenoceptors. In contrast, the cardio-selective antagonists betaxolol and atenolol have significant blocking actions of the isoproterenol response in the trachea. Selectivity indices for the compounds disclosed are for the most part impossible to calculate due to their cardiospecificity. For the more potent compounds, e.g. examples 1 and 4, the selectivities are 17000 and 45000 respectively whereas the selectivities for betaxolol and atenolol are 29 and 20 respectively. This indicates that the disclosed examples are to all intents and purposes highly potent cardiospecific β -adrenoceptor antagonists.

In pithed rat preparations many of the compounds can produce a 100% inhibition of the effects of isoproterenol administered in the dose of 0.1 ug/kg i.v. on heart rate but do not inhibit the fall in blood pressure produced by isoproterenol at doses as high as 300 ug/kg i.v. This fall in blood pressure largely

reflects a beta 2 effect of isoproterenol on peripheral blood vessels and is further proof of the high beta 1 selectivity of the compounds in vivo.

The high selectivity of blockade for these compounds is of major importance in the treatment of hypertension where exacerbation of an existing asthmatic condition may be precipitated by currently commercially available compounds. Highly selective compounds would be expected to have fewer adverse metabolic effects such as elevation of blood cholesterol and fewer vasospasm effects such as Raynaud's symptoms.

Some of the compounds also possess a degree of intrinsic sympathomimetic activity (ISA), a property which is useful in preventing undue bradycardia and helps reduce the incidence of heart failure in subjects with heart muscle disease. This property is also believed to be useful in reducing the incidence of rebound hypersensitivity occurring after cessation of beta blocking drugs which has been described with such drugs with no ISA like propranolol as well as reducing the incidence of adverse metabolic effects such as the elevated plasma cholesterol produced by drugs like propranolol which lack ISA.

This property can be demonstrated as an increase in resting heart rate in a pithed rat preparation using standard procedures in which the maximum effect of cumulative doses of drug up to 3 mg/kg are observed. Selected examples which show this activity are shown below:

Example No.	Maximum Change in Resting Heart Rate in the Pithed Rat
1	+ 101
5	+ 119
11	+ 66
13	+ 105
19	+ 51
23	+ 42
Propranolol	0
Atenolol	0
Betaxolol	0
Pindolol	+ 89

In some of these compounds the degree of beta agonist activity is such that when added to the selective beta antagonist properties the compounds are useful as cardiotonics e.g. for the treatment of heart insufficiency, especially in situations where a positive inotropic effect is desired without significant influence on blood pressure. The balance between the agonistic and antagonistic activities is particularly favourable for these compounds: the agonistic component contributes to the cardiotoxic activity while the antagonistic component protects against an excessive increase in contractile force which might lead to arrhythmias. Compounds in which R₂ is hydroxy show an added degree of partial agonist activity which is most useful in the treatment of cardiac insufficiency particularly in situations where a prolonged drug effect is not wanted.

These compounds also show the added advantage of lowering intraocular pressure when instilled as a buffered solution to the cornea of the eyes. Thus, those compounds can therefore be used for the treatment of glaucoma. This property can be demonstrated using a standard test in rabbits. Reductions in intraocular pressure are observed by as much as 4 mm Hg over a 2 hr period.

For these uses described above, the dose will vary according to the substance used, the mode of administration and the desired treatment. In general, however, the dose required to treat hypertension and related coronary heart diseases with an oral formulation of compounds 1 to 36 are obtained with a daily dosage of 0.5 to 5 mg per kg body weight: administration may be affected in 1, 2 or 3 divided doses or in a sustained release form. For larger mammals such as man the total daily dosage of these compounds is from about 1 to 600 mg; suitable pharmaceutical formulations for oral administration generally contain from 25 mg to 250 mg of the compounds together with solid or liquid carriers and/or diluents known to persons skilled in the art.

For the treatment of glaucoma the dose is usually administered as sterile eye drops as a 0.5 to 2 per cent solution in a buffered solution containing boric acid.

Claims

1. A compound of the formula I.

reflects a beta 2 effect of isoproterenol on peripheral blood vessels and is further proof of the high beta 1 selectivity of the compounds *in vivo*.

The high selectivity of blockade for these compounds is of major importance in the treatment of hypertension where exacerbation of an existing asthmatic condition may be precipitated by currently commercially available compounds. Highly selective compounds would be expected to have fewer adverse metabolic effects such as elevation of blood cholesterol and fewer vasospasm effects such as Raynaud's symptoms.

Some of the compounds also possess a degree of intrinsic sympathomimetic activity (ISA), a property which is useful in preventing undue bradycardia and helps reduce the incidence of heart failure in subjects with heart muscle disease. This property is also believed to be useful in reducing the incidence of rebound hypersensitivity occurring after cessation of beta blocking drugs which has been described with such drugs with no ISA like propranolol as well as reducing the incidence of adverse metabolic effects such as the elevated plasma cholesterol produced by drugs like propranolol which lack ISA.

This property can be demonstrated as an increase in resting heart rate in a pithed rat preparation using standard procedures in which the maximum effect of cumulative doses of drug up to 3 mg/kg are observed. Selected examples which show this activity are shown below:

Example No.	Maximum Change in Resting Heart Rate in the Pithed Rat
1	+ 101
5	+ 119
11	+ 86
13	+ 105
19	+ 51
23	+ 42
Propranolol	0
Atenolol	0
Betaxolol	0
Pindolol	+ 89

In some of these compounds the degree of beta agonist activity is such that when added to the selective beta antagonist properties the compounds are useful as cardiotonics e.g. for the treatment of heart insufficiency, especially in situations where a positive inotropic effect is desired without significant influence on blood pressure. The balance between the agonistic and antagonistic activities is particularly favourable for these compounds: the agonistic component contributes to the cardiotonic activity while the antagonistic component protects against an excessive increase in contractile force which might lead to arrhythmias. Compounds in which R₂ is hydroxy show an added degree of partial agonist activity which is most useful in the treatment of cardiac insufficiency particularly in situations where a prolonged drug effect is not wanted.

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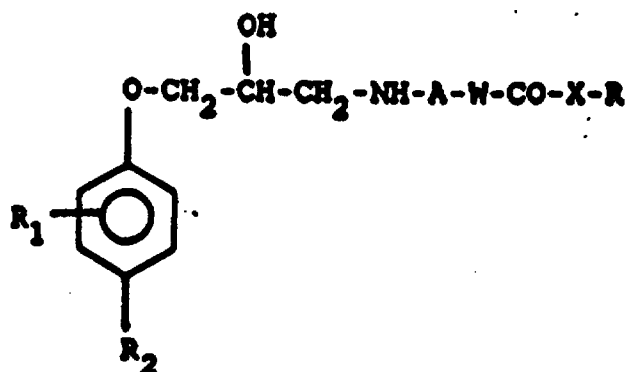
For these uses described above, the dose will vary according to the substance used, the mode of administration and the desired treatment. In general, however, the dose required to treat hypertension and related coronary heart diseases with an oral formulation of compounds 1 to 36 are obtained with a daily dosage of 0.5 to 5 mg per kg body weight: administration may be affected in 1, 2 or 3 divided doses or in a sustained release form. For larger mammals such as man the total daily dosage of these compounds is from about 1 to 600 mg; suitable pharmaceutical formulations for oral administration generally contain from 25 mg to 250 mg of the compounds together with solid or liquid carriers and/or diluents known to persons skilled in the art.

For the treatment of glaucoma the dose is usually administered as sterile eye drops as a 0.5 to 2 per cent solution in a buffered solution containing boric acid.

Claims

1. A compound of the formula I.





characterised in that

R represents furyl, pyranal, thienyl, pyrrolyl, indolyl, indolyl, hydroxyindolyl, purinyl hydroxy-purinyl, oxindolyl, indazolyl, isoindazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, quinolyl, quinolinonyl, isoquinolyl, isoquinolinonyl, quinazolyl or quinazolinonyl which is separated from the moiety X by a direct bond or an alkylene chain of 1 to 5 carbon atoms or an alkenylene chain of 2 to 5 carbon atoms and is optionally substituted with alkyl of 1 to 4 carbon atoms, or fused with phenyl or phenyl mono- or independently disubstituted with alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number 9 to 53, or any of the above unsaturated ring systems in partly saturated or fully saturated form, provided that R is not tetrahydropyranyl

R_1 represents hydrogen, hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, halogen of atomic number 9 to 53, trifluoromethyl, pyrrol-1-yl, cyano, carbamoyl, alkenyl of 2 to 5 carbon atoms, alkenyloxy of 2 to 5 carbon atoms wherein the double bond is at least one carbon removed from the oxygen, alkanoyl of 2 to 5 carbon atoms, nitro, amino, alkanoylamino of 1 to 5 carbon atoms in the alkanoyl moiety, R_2 represents a hydroxy group or a group $-Z-(CH_2)_n-Y-R_3$ wherein R_3 is hydrogen, alkyl or hydroxyalkyl of 1 to 5 carbon atoms, alkenyl of 3 to 7 carbon atoms in which the double bond is at least one carbon removed from Y , cycloalkyl or hydroxy substituted cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl or hydroxy substituted cycloalkylalkyl of 4 to 8 carbon atoms, phenyl or phenylalkyl of 6 to 10 carbon atoms in which the phenyl moiety can either be unsubstituted or

(i) monosubstituted with hydroxy, halogen, alkyl of 1 to 4 carbon atoms or carbamoyl,

(ii) independently disubstituted with hydroxy, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or carbamoyl,

Y represents oxygen or sulphur, and either

Z represents oxygen and n is 2 or 3, or

Z represents a bond and n is 1, 2 or 3,

A represents alkylene or branched alkylene of 2 to 5 carbon atoms,

W represents a bond or imino, and

X represents a bond or imino,

or a physiologically hydrolysable ester derivative thereof, in which at least one hydroxy group is in esterified form.

2. Compounds of claim 1 characterised in that

A is ethylene or trimethylene or branched trialkylene on the α -carbon to the nitrogen of the 3-aminopropoxy side chain such as $-CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$ or $-C(CH_3)_2(CH_2)_2-$.

W is imino,

X is imino or a bond,

R is a heterocyclic moiety connected to X by either a direct bond or a methylene moiety,

R_1 is substituted in the 2 position to the 3-aminopropoxy side chain, by hydrogen, hydroxy, cyano, halogen, carbamoyl, cycloalkyl or alkyl,

R_2 is a group $-Z-(CH_2)_n-Y-R_3$ in which R_3 is alkyl or hydroxyalkyl of 1 to 5 carbon atoms, cycloalkylalkyl or hydroxy substituted cycloalkylalkyl of up to 6 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl part, optionally substituted phenyl or



phenylalkyl with 1 to 3 carbon atoms in the alkyl portion,
 Y is an oxygen atom,
 Z is an oxygen atom, and
 n is 2.

3. Compounds as claimed in claim 2 characterised in that R is furyl, thienyl, indolyl, isoindazolyl, 2-oxo-1H-indolyl.

4. Compounds as claimed in claim 2 or 3 characterised in that R₁ is fluoro, cyano or methyl.

5. Compounds as claimed in any of claims 2 to 4 characterised in that R₂ is a group Z-(CH₂)_n-Y-R₃ in which R₃ is optionally substituted alkyl, optionally substituted cycloalkylalkyl, or optionally substituted phenyl or phenylalkyl with 1 to 3 carbon atoms in the alkyl portion in which substituents on the phenyl rings are hydroxy, methoxy, fluorine or methyl, and

Y is an oxygen atom,
 Z is an oxygen atom,
 n is 2.

6. Compounds of claim 1 characterised in that

A is ethylene or trimethylene or branched trialkylene on the α-carbon to the nitrogen of the 3-aminopropoxy side chain such as -CH(CH₃)CH₂-, -C(CH₃)₂CH₂- or -C(CH₃)₂(CH₂)₂-.

W is preferably imino,

X is imino or a bond

R is a heterocyclic moiety connected to X by either a direct bond or a methylene moiety

R₁ is substituted in the 2 position to the 3-aminopropoxy side chain, by hydrogen, hydroxy, cyano, halogen, carbamoyl, cycloalkyl or alkyl, and

R₂ is hydroxy

and physiologically hydrolysable ester derivatives thereof having at least one hydroxy group in esterified form.

7. Compounds as claimed in claim 6 characterised in that R is furyl, thienyl, indolyl, isoindazolyl or 2-oxo-1H-indolyl.

8. Compounds of claim 1 characterised in that A, R, R₂ and R₁ are as defined in claims 3, 4 and 5 and where W is a bond, and X is imino, and physiologically hydrolysable ester derivatives thereof having at least one hydroxy group in esterified form.

9. Compounds of claim 1 characterised in that R₁, A, R and R₂ are as defined in claim 3, 4 and 5 and where X and W are imino or a bond, and physiologically hydrolysable ester derivatives thereof having at least one hydroxy group in esterified form.

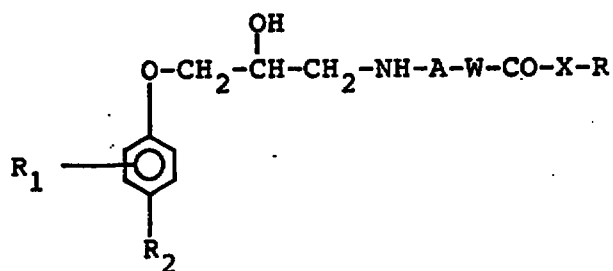
10. Compounds of claim 1 characterised in that R₁, A and R are as defined in claim 3, 4 and 5 and where W and X are imino or a bond and where R₂ is hydroxy.

11. Compounds of claim 1 characterised in that R₁, A and R are as defined in claims 3, 4 and 5 and where W is a bond, X is imino and where R₂ is hydroxy.

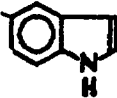
12. Compounds as claimed in any one of the preceding claims which are in the optically active (S)- form at the carbon atom in the 2-position of the 3-aminopropoxy side chain.

13. A compound of the formula I

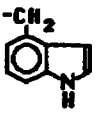
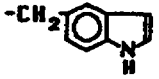
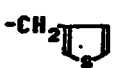
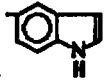
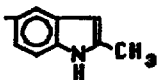
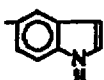




in which groups R_2 is $-\text{Z}(\text{CH}_2)_n-\text{Y}-\text{R}_3$ and R_1 , A, W, X, R, R_3 , Z, Y and n are selected from the following combinations:

Example No.	A	W	X	R	$\text{R}_1^{a)}$	R_3	Y	Z	n
1	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
2	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	Bond	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
3	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	Bond	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
4	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
5	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
6	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	-NH-		o-CN	$-\text{CH}_2-$ 	0	0	2
7	$-\text{CH}(\text{CH}_2)_2-\text{CH}(\text{CH}_2)_2-$	-NH-	-NH-		o-CN	Pr	0	0	2



Example No.	A	W	X	R	R ₁	R ₃	Y	Z	n
8	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2
9	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2
10	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2
11	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2
12	$\text{-C(Me)CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2
13	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	Bu	0	0	2
14	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{CH}_2\text{-}$ 	0	0	2
15	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{CH}_2\text{-}$ 	0	0	2
16	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2
17	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		H	Pr	0	0	2
18	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2
19	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{-}$ 	0	0	2
20	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-CN	Pr	0	0	2
21	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		H	$\text{-CH}_2\text{-}$ 	0	0	2
22	$\text{-CH}_2\text{CH}_2\text{-}$	-NH-	Bond		o-Br	$\text{-CH}_2\text{-}$ 	0	0	2



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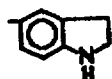
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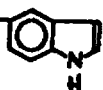
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Example No.	A	W	X	R	R ₁	R ₃	Y	Z	n
23	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	$\text{-CH}_2\text{-}$ 	0	0	2
24	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	$\text{-CH}_2\text{-}$ 	0	0	2
b) 25	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R,S) 2	-NH-	Bond		H	Pr	0	0	2
26	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	Pr	0	0	2
27	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		o-Br	Pr	0	0	2
28	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	Pr	0	0	2
c) 29	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R) 2	-NH-	Bond		H	Pr	0	0	2
d) 30	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R) 2	-NH-	Bond		H	2-Me-Pr	0	0	2
e) 31	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R) 2	-NH-	Bond		H	$\text{-CH}_2\text{-}$ 	0	0	2
32	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	2-Me-Pr	0	0	2
f) 33	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R) 2	-NH-	Bond		o-F	Pr	0	0	2
g) 34	$\text{-CH(CH}_3\text{)-CH}_2\text{-}$ (R) 2	-NH-	Bond		o-F	2-Me-Pr	0	0	2
35	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	Pr	0	0	2
36	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	Pr	0	0	2
37	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bond		H	$\text{-CH}_2\text{-}$ 	0	0	2



Example No.	A	W	X	R	R ₁	R ₃	Y	Z	n
38	(CH ₂) ₃	bond	-NH-		o-CN	Pr	0	0	2
39	-(CH ₂) ₂ -	bond	NH		o-CN	Pr	0	0	2

a) o indicates ortho to the 3-aminopropoxy side chain

(b) Mixture of 2 diastereomers with the S-configuration on the carbon atom in the 2-position of the 3-amino propoxy side chain; $[\alpha]_D^{20} = -6.64^\circ$ (c = 1.58/MeOH).

(c) Mixture of 2 diastereomers with the R configuration on the carbon atom of the group A bond to the nitrogen; $[\alpha]_D^{20} = -8.04^\circ$ (c = 1.9/MeOH).

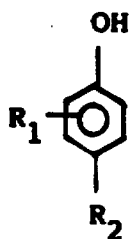
(d) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = 11.43^\circ$ (c = 1.0/MeOH).

(e) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.2^\circ$ (c = 1.22/MeOH).

(f) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.1^\circ$ (c = 1.57/MeOH).

(g) Mixture of 2 diastereomers with the R configuration of the carbon atom of the group A; $[\alpha]_D^{20} = -7.30^\circ$ (c = 0.8/MeOH).

14. A process for the preparation of a compound of Formula I as stated and defined in claims 1 to 13 characterised by the step of appropriately 3-amino-2-oxypropylating a corresponding compound of Formula II,

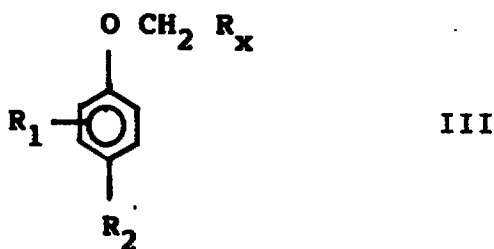


II

wherein R₁ and R₂ are as defined in any preceding claim, or a precursor form thereof.



15. A process for the preparation of a compound of Formula I as claimed in claim 1 to 13, characterised in that in a first process stage a group $\text{CH}_2\text{-R}_x$, wherein R_x is a group capable of reacting with a primary amine to give a 2-amino-1-hydroxyethyl group, is introduced by O-alkylation in the 1 position into a compound of Formula II to give a corresponding compound of Formula III,



wherein R_1 and R_2 are as defined in any of claims 1 to 13, and in a second process stage the compound of Formula III is animated with a corresponding compound of Formula IV,

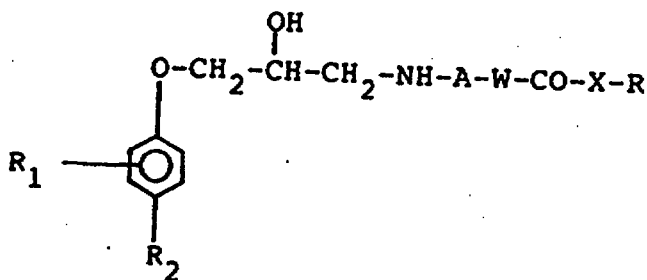


wherein A, W, X and R are as defined in any of claims 1 to 13, and, where required, having at least one hydroxy group in a resultant compound of Formula I in appropriately esterified form.

16. A pharmaceutical composition characterised in that it comprises a compound of any one of claims 1 to 13 in free form or in a pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.
17. The use of a compound as claimed in any one of claims 1 to 13 in the manufacture of a composition for use in a method of treatment of human or animal body, preferably for use in the prophylaxis or therapy of diseases which are commonly known to respond to blockade of beta adrenoceptors such as those found in the heart including hypertension, myocardial infarction, sympathetic overstimulation, migraine, glaucoma, thyrotoxicosis, heart rhythm disorders and cardiac failure.

Patentansprüche

1. Verbindung der Formel I



dadurch gekennzeichnet, daß

R Furyl, Pyranyl, Thienyl, Pyrrolyl, Indolyl, Indoliny, Hydroxyindoliny, Puriny, Hydroxypuriny, Oxindolyl, Indazolyl, Isoindazolyl, Benzimidazolyl, Benzimidazolonyl, Benztriazolyl, Chinoliny, Chinolinonyl, Isochinoliny, Isochinolinonyl, Chinazoliny oder Chinazolinonyl darstellt, das von der Einheit X durch eine direkte Bindung oder eine Alkylenkette mit 1 bis 5 Kohlenstoffatomen oder eine Alkenylenkette mit 2 bis 5 Kohlenstoffatomen getrennt ist und gegebenenfalls mit Alkyl mit 1 bis 4 Kohlenstoffatomen substituiert ist oder mit Phenyl oder Phenyl, welches einfach oder unabhängig zweifach mit Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Halogen der Ordnungszahl 9 bis 53 oder irgendeinem der obigen nicht-gesättigten Ringsysteme in teilweise gesättigter oder voll gesättigter Form substituiert



ist, mit der Maßgabe, daß R nicht Tetrahydropyranyl ist, kondensiert ist;

R₁ Wasserstoff, Hydroxy, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen, Alkylthio mit 1 bis 4 Kohlenstoffatomen, Cycloalkyl mit 3 bis 7 Kohlenstoffatomen, Halogen der Ordnungszahl 9 bis 53, Trifluormethyl, Pyrol-1-yl, Cyano, Carbamoyl, Alkenyl mit 2 bis 5 Kohlenstoffatomen, Alkenyloxy mit 2 bis 5 Kohlenstoffatomen, worin die Doppelbindung mindestens 1 Kohlenstoff vom Sauerstoff entfernt ist, Alkanoyl mit 2 bis 5 Kohlenstoffatomen, Nitro, Amino, Alkanoylamino mit 1 bis 5 Kohlenstoffatomen in der Alkanoyleinheit, darstellt;

R₂ eine Hydroxygruppe oder ein Gruppe $-Z-(CH_2)_n-Y-R_3$ darstellt, worin R₃ Wasserstoff, Alkyl oder Hydroxyalkyl mit 1 bis 5 Kohlenstoffatomen, Alkenyl mit 3 bis 7 Kohlenstoffatomen, worin die Doppelbindung mindestens 1 Kohlenstoff von Y entfernt ist, Cycloalkyl oder Hydroxy-substituiertes Cycloalkyl mit 3 bis 7 Kohlenstoffatomen, Cycloalkylalkyl oder Hydroxy-substituiertes Cycloalkylalkyl mit 4 bis 8 Kohlenstoffatomen, Phenyl oder Phenylalkyl mit 6 bis 10 Kohlenstoffatomen, worin die Phenyleinheit entweder unsubstituiert oder

(i) mit Hydroxy, Halogen, Alkyl mit 1 bis 4 Kohlenstoffatomen oder Carbamoyl monosubstituiert,

(ii) unabhängig mit Hydroxy, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Carbamoyl disubstituiert

sein kann, ist,

Y Sauerstoff oder Schwefel darstellt, und entweder

Z Sauerstoff darstellt und n 2 oder 3 ist oder

Z eine Bindung darstellt und n 1, 2 oder 3 ist;

A Alkylen oder verzweigtes Alkylen mit 2 bis 5 Kohlenstoffatomen darstellt,

W eine Bindung oder Imino darstellt und

X eine Bindung oder Imino darstellt,

oder ein physiologisch hydrolysierbares Esterderivat davon, in dem mindestens eine Hydroxygruppe in veresterter Form vorliegt.

2. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß

A Ethylen oder Trimethylen oder verzweigtes Trialkylen am α -Kohlenstoff des Stickstoffs der 3-Aminopropoxy-Seitenkette, wie z.B. $-CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$ oder $-C(CH_3)_2(CH_2)_2-$, ist,

W Imino ist,

X Imino oder eine Bindung ist,

R eine heterocyclische Einheit, die entweder durch eine direkte Bindung oder eine Methyleneinheit mit X verbunden ist, ist,

R₁ in der 2-Stellung zur 3-Aminopropoxy-Seitenkette mit Wasserstoff, Hydroxy, Cyano, Halogen, Carbamoyl, Cycloalkyl oder Alkyl substituiert ist,

R₂ eine Gruppe $Z-(CH_2)_n-Y-R_3$ ist, worin R₃ Alkyl oder Hydroxyalkyl mit 1 bis 5 Kohlenstoffatomen, Cycloalkylalkyl oder Hydroxy-substituiertes Cycloalkylalkyl mit bis zu 6 Kohlenstoffatomen in der Cycloalkyleinheit und 1 bis 3 Kohlenstoffatomen im Alkylteil, gegebenenfalls substituiertes Phenyl oder Phenylalkyl mit 1 bis 3 Kohlenstoffatomen im Alkylteil ist,

Y ein Sauerstoffatom ist,

Z ein Sauerstoffatom ist und

n 2 ist.

3. Verbindungen, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß R Furyl, Thienyl, Indolyl, Isoindazolyl, 2-Oxo-1H-indolyl ist.

4. Verbindungen, wie in Anspruch 2 oder 3 beansprucht, dadurch gekennzeichnet, daß R₁ Fluor, Cyano oder Methyl ist.

5. Verbindungen, wie in irgendeinem der Ansprüche 2 bis 4 beansprucht, dadurch gekennzeichnet, daß R₂ eine Gruppe $Z-(CH_2)_n-Y-R_3$ ist, worin R₃ gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Cycloalkylalkyl oder gegebenenfalls substituiertes Phenyl oder Phenylalkyl mit 1 bis 3 Kohlenstoffatomen im Alkylteil ist, worin Substituenten an den Phenylringen Hydroxy, Methoxy, Fluor oder Methyl sind, und

Y ein Sauerstoffatom ist,

Z ein Sauerstoffatom ist,



n 2 ist.

6. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß

- A Ethylen oder Trimethylen oder verzweigtes Trialkylen am α -Kohlenstoff des Stickstoffs der 3-Aminopropoxyseitenkette, wie z.B. $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$ oder $-\text{C}(\text{CH}_3)_2(\text{CH}_2)_2-$, ist
 W vorzugsweise Imino ist,
 X Imino oder eine Bindung ist,
 R eine heterocyclische Einheit, die entweder durch eine direkte Bindung oder eine Methyleinheit mit X verbunden ist, ist,
 R₁ in der 2-Stellung zur 3-Aminopropoxyseitenkette durch Wasserstoff, Hydroxy, Cyano, Halogen, Carbamoyl, Cycloalkyl oder Alkyl substituiert ist und
 R₂ Hydroxy ist,

und physiologisch hydrolysierbare Esterderivate davon, die mindestens eine Hydroxygruppe in veresterter Form aufweisen.

7. Verbindungen wie in Anspruch 6 beansprucht, dadurch gekennzeichnet, daß R Furyl, Thienyl, Indolyl, Isoindazolyl oder 2-Oxo-1H-indolyl ist.

8. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß A, R, R₂ und R₁ wie in den Ansprüchen 3, 4 und 5 definiert sind, und worin W eine Bindung ist und X Imino ist, und physiologisch hydrolysierbare Esterderivate davon, die mindestens eine Hydroxygruppe in veresterter Form aufweisen.

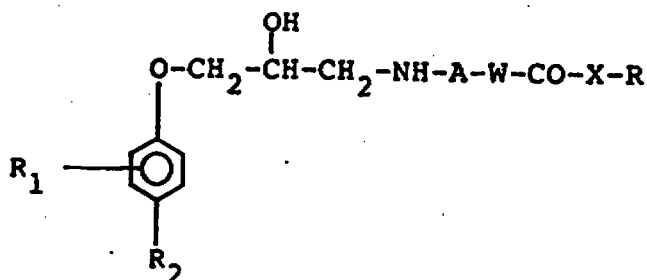
9. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß R₁, A, R und R₂ wie in den Ansprüchen 3, 4 und 5 definiert sind, und worin X und W Imino oder eine Bindung sind, und physiologisch hydrolysierbare Esterderivate davon, die mindestens eine Hydroxygruppe in veresterter Form aufweisen.

10. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß R₁, A und R wie in den Ansprüchen 3, 4 und 5 definiert sind, und worin W und X Imino oder eine Bindung sind und worin R₂ Hydroxy ist.

11. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß R₁, A und R wie in den Ansprüchen 3, 4 und 5 definiert sind, und worin W eine Bindung ist, X Imino ist und worin R₂ Hydroxy ist.

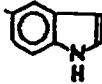
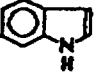
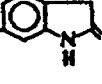
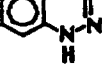
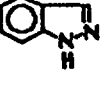
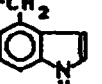
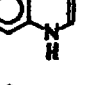
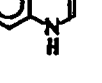
12. Verbindungen, wie in irgendeinem der vorangehenden Ansprüche beansprucht, die am Kohlenstoffatom in der 2-Stellung der 3-Aminopropoxy-Seitenkette in der optisch aktiven (S)-Form vorliegen.

13. Verbindung der Formel I

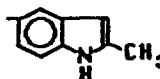


worin die Gruppe R₂ $-\text{Z}-(\text{CH}_2)_n-\text{Y}-\text{R}_3$ ist und R₁, A, W, X, R, R₃, Z, Y und n aus den folgenden Kombinationen ausgewählt sind:

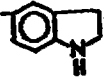
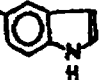
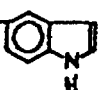


Beispiel Nr.	A	W	X	R	R ₁ ^{a)}	R ₃	Y	Z	n
1	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Pr	0	0	2
2	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bin- dung	$-CH_2-$ 	o-CN	Pr	0	0	2
3	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bin- dung	$-CH_2-$ 	o-CN	Pr	0	0	2
4	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Pr	0	0	2
5	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Pr	0	0	2
6	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	$-CH_2-$ 	0	0	2
7	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Pr	0	0	2
8	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bindung	$-CH_2-$ 	o-CN	Pr	0	0	2
9	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bindung	$-CH_2-$ 	o-CN	Pr	0	0	2
10	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bindung	$-CH_2-$ 	o-CN	Pr	0	0	2
11	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	Bindung	$-CH_2-$ 	o-CN	Pr	0	0	2
12	$\begin{smallmatrix} -C(Me) & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Pr	0	0	2
13	$\begin{smallmatrix} -CH & CH - \\ 2 & 2 \end{smallmatrix}$	-NH-	-NH-		o-CN	Bu	0	0	2



Beispiel Nr.	A	W	X	R	R ₄	R ₃	Y	Z	n
14	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{-CH}_2\text{-}$ 	0	0	2
15	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{-CH}_2\text{-}$ 	0	0	2
16	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2
17	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		H	Pr	0	0	2
18	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	Pr	0	0	2
19	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	-NH-		o-CN	$\text{-CH}_2\text{-}$ 	0	0	2
20	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bindung		o-CN	Pr	0	0	2
21	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bindung		H	$\text{-CH}_2\text{-}$ 	0	0	2
22	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bindung		o-Br	$\text{-CH}_2\text{-}$ 	0	0	2
23	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bindung		H	$\text{-CH}_2\text{-}$ 	0	0	2
24	$\text{-CH}_2\text{-CH}_2\text{-}$	-NH-	Bindung		H	$\text{-CH}_2\text{-}$ 	0	0	2
b) 25	$\text{-CH}_2\text{-CH}_2\text{-}$ (R,S) 2	-NH-	Bindung		H	Pr	0	0	2

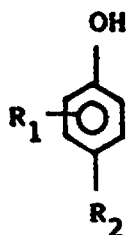


Beispiel Nr.	A	W	X	R	R ₁	R ₃	Y	Z	n
26	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	Pr	0	0	2
27	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		o-Br	Pr	0	0	2
28	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	Pr	0	0	2
c) 29	$\begin{smallmatrix} CH_3 \\ \\ -CH-CH- \\ (R) & 2 \end{smallmatrix}$	-NH-	Bindung		H	Pr	0	0	2
d) 30	$\begin{smallmatrix} CH_3 \\ \\ -CH-CH- \\ (R) & 2 \end{smallmatrix}$	-NH-	Bindung		H	2-Me-Pr	0	0	2
e) 31	$\begin{smallmatrix} CH_3 \\ \\ -CH-CH- \\ (R) & 2 \end{smallmatrix}$	-NH-	Bindung		H	$\begin{smallmatrix} -CH \\ 2 \end{smallmatrix}$ 	0	0	2
32	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	2-Me-Pr	0	0	2
f) 33	$\begin{smallmatrix} CH_3 \\ \\ -CH-CH- \\ (R) & 2 \end{smallmatrix}$	-NH-	Bindung		o-F	Pr	0	0	2
g) 34	$\begin{smallmatrix} CH_3 \\ \\ -CH-CH- \\ (R) & 2 \end{smallmatrix}$	-NH-	Bindung		o-F	2-Me-Pr	0	0	2
35	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	Pr	0	0	2
36	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	Pr	0	0	2
37	$\begin{smallmatrix} -CH & CH - \\ & 2 & 2 \end{smallmatrix}$	-NH-	Bindung		H	$\begin{smallmatrix} -CH \\ 2 \end{smallmatrix}$ 	0	0	2
38	$(CH_2)_3$	Bindung	-NH-		o-CN	Pr	0	0	2
39	$-(CH_2)_2-$	Bindung	NH		o-CN	Pr	0	0	2



- a) o zeigt ortho-Stellung zur 3-Aminopropoxy-Seitenkette an.
- b) Mischung von 2 Diastereomeren mit der S-Konfiguration am Kohlenstoffatom in der 2-Stellung der 3-Aminopropoxy-Seitenkette; $[\alpha]_D^{20} = -6,64^\circ$ ($c = 1,58/\text{MeOH}$).
- c) Mischung von 2 Diastereomeren mit der R-Konfiguration am Kohlenstoffatom der Gruppe A, der an den Stickstoff gebunden ist; $[\alpha]_D^{20} = -8,04^\circ$ ($c = 1,9/\text{MeOH}$).
- d) Mischung von 2 Diastereomeren mit der R-Konfiguration am Kohlenstoffatom der Gruppe A; $[\alpha]_D^{20} = 11,43^\circ$ ($c = 1,0/\text{MeOH}$).
- e) Mischung von 2 Diastereomeren mit der R-Konfiguration am Kohlenstoffatom der Gruppe A; $[\alpha]_D^{20} = -7,2^\circ$ ($c = 1,22/\text{MeOH}$).
- f) Mischung von 2 Diastereomeren mit der R-Konfiguration am Kohlenstoffatom der Gruppe A; $[\alpha]_D^{20} = -7,1^\circ$ ($c = 1,57/\text{MeOH}$).
- g) Mischung von 2 Diastereomeren mit der R-Konfiguration am Kohlenstoffatom der Gruppe A; $[\alpha]_D^{20} = -7,30^\circ$ ($c = 0,8/\text{MeOH}$).

14. Verfahren zur Herstellung einer Verbindung der Formel I, wie in den Ansprüchen 1 bis 13 aufgeführt und definiert, gekennzeichnet durch die Stufe geeigneter 3-Amino-2-oxypropylierung einer entsprechenden Verbindung der Formel II,



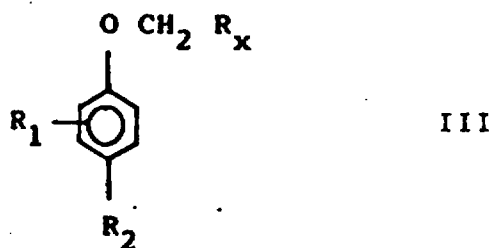
II

worin R₁ und R₂ wie in irgendeinem der vorangehenden Ansprüche definiert sind, oder einer Vorläuferform davon.

15. Verfahren zur Herstellung einer Verbindung der Formel I, wie in den Ansprüchen 1 bis 13 beansprucht, dadurch gekennzeichnet, daß in einer ersten Verfahrensstufe eine Gruppe CH₂-R_x, worin R_x eine Gruppe ist, die in der Lage ist, mit einem primären Amin zu reagieren, um eine 2-Amino-1-hydroxyethyl-Gruppe zu ergeben, durch O-Alkylierung an der 1-Stellung in eine Verbindung der Formel



II eingeführt wird, um eine entsprechende Verbindung der Formel III



15 zu ergeben, worin R_1 und R_2 wie in irgendeinem der Ansprüche 1 bis 13 definiert sind, und in einer zweiten Verfahrensstufe die Verbindung der Formel III mit einer entsprechenden Verbindung der Formel IV



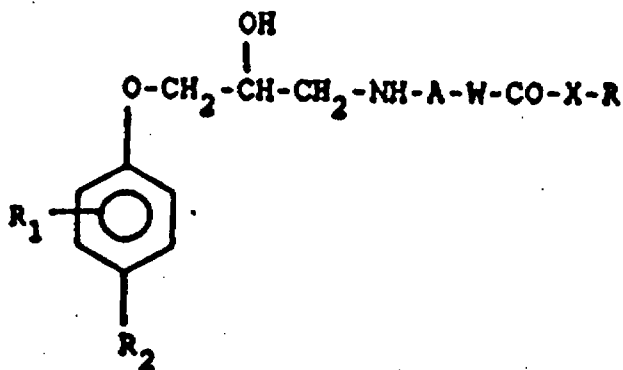
20 worin A, W, X und R wie in irgendeinem der Ansprüche 1 bis 13 definiert sind, aktiviert wird, und, wo erforderlich, mindestens eine Hydroxygruppe in einer resultierenden Verbindung der Formel I in geeignet veresterter Form vorliegt.

25 16. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie eine Verbindung nach irgendeinem der Ansprüche 1 bis 13 in freier Form oder in Form eines pharmazeutisch annehmbaren Salzes in Verbindung mit einem pharmazeutischen Träger oder Verdünnungsmittel umfaßt.

30 17. Verwendung einer Verbindung, wie in irgendeinem der Ansprüche 1 bis 13 beansprucht, bei der Herstellung einer Zusammensetzung zur Verwendung in einem Verfahren zur Behandlung des menschlichen oder tierischen Körpers, vorzugsweise zur Verwendung bei der Prophylaxe oder Therapie von Krankheiten, von denen allgemein bekannt ist, daß sie auf die Blockade von beta-Adrenozeptoren, wie z.B. jenen, die im Herzen gefunden werden, ansprechen, einschließlich Bluthochdruck, Myokardinfarkt, sympathischer Überstimulierung, Migräne, Glaukom, Thyrotoxikose, Herzrhythmusstörungen und Herzversagen.

Revendications

1. Composé de formule I :



caractérisé en ce que

55 R représente un groupe furyle, pyrannyle, thiényle, pyrrolyle, indolye, indolinye, hydroxyindolinye, purinye, hydroxypurinye, oxindolyle, indazolyle, isoindazolyle, benzimidazolyle, benzimidazolonye, benzotriazolyle, quinoléinye, quinoléinonye, isoquinoléinye, isoquinoléinonye, quinazolinye ou quina-



atomes de carbone ou par une chaîne alcénylène de 2 à 5 atomes de carbone, et qui est éventuellement substitué par un reste alkyle ayant 1 à 4 atomes de carbone, ou bien qui est condensé sur le noyau phényle ou sur un noyau phényle monosubstitué ou disubstitué, de manière indépendante, par un groupe alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 4 atomes de carbone ou 1 atome d'halogène dont le nombre atomique se situe entre 9 et 53, ou n'importe lequel des systèmes cycliques insaturés ci-dessus sous forme partiellement saturée ou entièrement saturée, à la condition que R ne représente pas un groupe tétrahydropyrannyle ;

R₁ représente un atome d'hydrogène, un groupe hydroxyle, alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 4 atomes de carbone, alkylthio ayant 1 à 4 atomes de carbone, cycloalkyle ayant 3 à 7 atomes de carbone, un atome d'halogène dont le nombre ou numéro atomique va de 9 à 53, un groupe trifluorométhyle, pyrrolyle-(1), cyano, carbamoyle, alcényle ayant 2 à 5 atomes de carbone, alcényloxy ayant 2 à 5 atomes de carbone, dans lequel la double liaison est séparée de l'oxygène par au moins un atome de carbone, un groupe alcanoyle de 2 à 5 atomes de carbone, un groupe nitro, amino, alcanoylamino ayant 1 à 5 atomes de carbone dans le fragment alcanoyle ;

R₂ représente un groupe hydroxyle ou un groupe -Z-(CH₂)_n-Y-R₃, dans lequel R₃ représente un atome d'hydrogène, un groupe alkyle ou hydroxyalkyle ayant 1 à 5 atomes de carbone, alcényle ayant 3 à 7 atomes de carbone, dans lequel la double liaison est séparée de Y par au moins un atome de carbone, un groupe cycloalkyle ou cycloalkyle à substituant hydroxyle ayant 3 à 7 atomes de carbone, un groupe cycloalkylalkyle ou cycloalkylalkyle à substituant hydroxyle, ayant 4 à 8 atomes de carbone, un groupe phényle ou phénylalkyle ayant 6 à 10 atomes de carbone et dans lequel le fragment phényle peut être non substitué ou bien

(i) monosubstitué par un reste hydroxyle, halogéno, alkyle ayant 1 à 4 atomes de carbone ou carbamoyle,

(ii) disubstitué, indépendamment, par un groupe hydroxyle, alkyle ayant 1 à 4 atomes de carbone, alcoxy ayant 1 à 4 atomes de carbone ou carbamoyle,

Y représente un atome d'oxygène ou de soufre, et

Z représente un atome d'oxygène et n vaut 2 ou 3, ou bien

Z représente une liaison (directe) et n vaut 1, 2 ou 3,

A représente un groupe alkylène ou alkylène ramifié ayant 2 à 5 atomes de carbone,

W représente une liaison (directe) ou un groupe imino, et

X représente une liaison ou un groupe imino,

ou un ester physiologiquement hydrolysable, dérivant de ce composé et dans lequel au moins un groupe hydroxyle est sous forme estérifiée.

2. Composés selon la revendication 1, caractérisés en ce que :

A représente un groupe éthylène ou triméthylène ou trialkylène ramifié fixé sur l'atome de carbone en α de l'azote de la chaîne latérale 3-aminopropoxy, comme un groupe -CH(CH₃)CH₂-, -C(CH₃)₂CH₂- ou -C(CH₃)₂(CH₂)₂- ;

W représente un groupe imino,

X représente un groupe imino ou une liaison (directe),

R représente un fragment hétérocyclique relié à X par une liaison directe ou par un fragment méthylène,

R₁ porte comme substituant, sur la position 2 par rapport à la chaîne latérale 3-aminopropoxy, un atome d'hydrogène, un groupe hydroxyle, cyano, halogéno, carbamoyle, cycloalkyle ou alkyle,

R₂ représente un groupe Z-(CH₂)_n-Y-R₃, dans lequel R₃ représente un groupe alkyle ou hydroxyalkyle ayant 1 à 5 atomes de carbone, cycloalkylalkyle ou cycloalkylalkyle à substituant hydroxyle, ayant jusqu'à 6 atomes de carbone dans le fragment cycloalkyle et 1 à 3 atomes de carbone dans la partie alkylique, un groupe phényle ou phénylalkyle éventuellement substitué et comportant 1 à 3 atomes de carbone dans la partie alkyle,

Y représente un atome d'oxygène,

Z représente un atome d'oxygène, et n vaut 2.

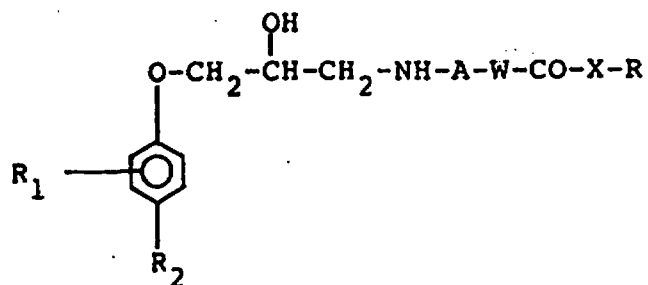
3. Composés tels que revendiqués à la revendication 2, caractérisés en ce que R représente un groupe furyle, thiényle, indolye, isoindazolyle, 2-oxo-1H-indolye.

4. Composés tels que revendiqués à la revendication 2 ou 3, caractérisés en ce que R₁ représente un groupe fluoro, cyano ou méthyle.

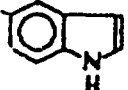
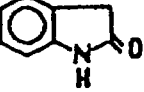
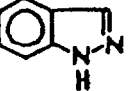


5. Composés tels que revendiqués dans l'une quelconque des revendications 2 à 4, caractérisés en ce que R_2 représente un groupe $Z-(CH_2)_n-Y-R_3$, dans lequel R_3 représente un groupe alkyle éventuellement substitué, un groupe cycloalkylalkyle éventuellement substitué ou un groupe phényle ou phénylalkyle éventuellement substitué et comportant 1 à 3 atomes de carbone dans la partie alkyle, les substituants fixés sur le ou les noyaux phényles étant un groupe hydroxyle, méthoxy, fluoro ou méthyle,
 Y représente un atome d'oxygène,
 Z représente un atome d'oxygène,
 n vaut 2.
6. Composés selon la revendication 1, caractérisés en ce que
 A représente un groupe éthylène ou triméthylène ou trialkylène ramifié sur l'atome de carbone en α de l'azote de la chaîne latérale 3-aminopropoxy, tel qu'un groupe $-CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$ ou $-C(CH_3)_2(CH_2)_2-$;
 W est de préférence un groupe imino,
 X représente un groupe imino ou une liaison (directe),
 R représente un fragment hétérocyclique relié à X par une liaison directe ou par un fragment méthylène,
 R_1 est substitué sur la position 2 par rapport à la chaîne latérale 3-aminopropoxy, et porte ainsi un atome d'hydrogène, un groupe hydroxyle, cyano, halogéno, carbamoyle, cycloalkyle ou alkyle, et
 R_2 représente un groupe hydroxyle,
 et les esters physiologiquement hydrolysables qui en dérivent et qui comportent au moins un groupe hydroxyle sous forme estérifiée.
7. Composés tels que revendiqués à la revendication 6, caractérisés en ce que R représente un groupe furyle, thiényle, indolye, isoindazolyle ou 2-oxo-1H-indolye.
8. Composés selon la revendication 1, caractérisés en ce que A, R, R_2 et R_1 sont tels que définis aux revendications 3, 4 et 5, et W représente une liaison (directe) et X représente un groupe imino, et les esters physiologiquement hydrolysables qui en dérivent et qui comportent au moins un groupe hydroxyle sous forme estérifiée.
9. Composés selon la revendication 1, caractérisés en ce que R_1 , A, R et R_2 sont tels que définis aux revendications 3, 4 et 5, et X et W représentent chacun un groupe imino ou une liaison directe, et les esters physiologiquement hydrolysables qui en dérivent et qui comportent au moins un groupe hydroxyle sous forme estérifiée.
10. Composés selon la revendication 1, caractérisés en ce que R_1 , A et R sont tels que définis aux revendications 3, 4 et 5, et les symboles W et X représentent chacun un groupe imino ou une liaison, et R_2 représente un groupe hydroxyle.
11. Composés selon la revendication 1, caractérisés en ce que R_1 , A et R sont tels que définis aux revendications 3, 4 et 5, et W représente une liaison, X représente un groupe imino et R_2 représente un groupe hydroxyle.
12. Composés tels que revendiqués dans l'une quelconque des revendications précédentes, qui sont sous forme optiquement active (S) sur l'atome de carbone en position 2 de la chaîne latérale 3-aminopropoxy.
13. Composé de formule I

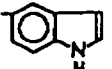
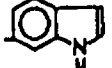
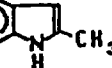




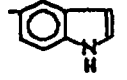
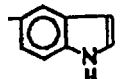
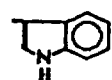
dans laquelle les groupes R_2 représentent $-\text{Z}(\text{CH}_2)_n-\text{Y}-\text{R}_3$ et les symboles R_1 , A , W , X , R , R_3 , Z , Y et n sont choisis parmi les combinaisons suivantes :

Exemple n°	A	W	X	R	R_1 ^{a)}	R_3	Y	Z	n
1	$-\text{CH}_2-\text{CH}_2-$	$-\text{NH}-$	$-\text{NH}-$		$\text{o}-\text{CN}$	Pr	0	0	2
2	$-\text{CH}_2-\text{CH}_2-$	$-\text{NH}-$	liaison	$-\text{CH}_2-$ 	$\text{o}-\text{CN}$	Pr	0	0	2
3	$-\text{CH}_2-\text{CH}_2-$	$-\text{NH}-$	liaison	$-\text{CH}_2-$ 	$\text{o}-\text{CN}$	Pr	0	0	2
4	$-\text{CH}_2-\text{CH}_2-$	$-\text{NH}-$	$-\text{NH}-$		$\text{o}-\text{CN}$	Pr	0	0	2

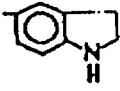
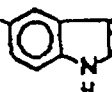
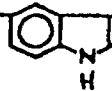


Exemple n°	A	W	X	R	R ₁	R ₃	Y	Z	n
5	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
6	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	$-\text{CH}_2-$ 	0	0	2
7	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
8	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
9	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
10	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
11	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison	$-\text{CH}_2-$ 	o-CN	Pr	0	0	2
12	$-\text{C}(\text{Me})_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
13	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Bu	0	0	2
14	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	$-\text{CH}_2-\text{CH}_2-$ 	0	0	2
15	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	$-\text{CH}_2-\text{CH}_2-$ 	0	0	2
16	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
17	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		H	Pr	0	0	2



Exemple n°	A	W	X	R	R ₁	R ₃	Y	Z	n
18	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	Pr	0	0	2
19	$-\text{CH}_2-\text{CH}_2-$	-NH-	-NH-		o-CN	$-\text{CH}_2-\text{C}_6\text{H}_4\text{F}$	0	0	2
20	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		o-CN	Pr	0	0	2
21	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	$-\text{CH}_2-\triangle$	0	0	2
22	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		o-Br	$-\text{CH}_2-\triangle$	0	0	2
23	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	$-\text{CH}_2-\triangle$	0	0	2
24	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	$-\text{CH}_2-\triangle$	0	0	2
b) 25	$\begin{matrix} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}, \text{S}) \quad 2 \end{matrix}$	-NH-	liaison		H	Pr	0	0	2
26	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	Pr	0	0	2
27	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		o-Br	Pr	0	0	2
28	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	Pr	0	0	2
c) 29	$\begin{matrix} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}) \quad 2 \end{matrix}$	-NH-	liaison		H	Pr	0	0	2
d) 30	$\begin{matrix} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}) \quad 2 \end{matrix}$	-NH-	liaison		H	2-Me-Pr	0	0	2



Exemple n°	A	W	X	R	R ₁	R ₃	Y	Z	n
31 ^{e)}	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}) \quad 2 \end{array}$	-NH-	liaison		H	$-\text{CH}_2$ 	0	0	2
32	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	2-Me-Pr	0	0	2
33 ^{f)}	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}) \quad 2 \end{array}$	-NH-	liaison		o-F	Pr	0	0	2
34 ^{g)}	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}- \\ \quad \\ (\text{R}) \quad 2 \end{array}$	-NH-	liaison		o-F	2-Me-Pr	0	0	2
35	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	Pr	0	0	2
36	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	Pr	0	0	2
37	$-\text{CH}_2-\text{CH}_2-$	-NH-	liaison		H	$-\text{CH}_2$ 	0	0	2
38	$(\text{CH}_2)_3$	liaison	NH		o-CN	Pr	0	0	2
39	$-(\text{CH}_2)_2-$	liaison	NH		o-CN	Pr	0	0	2

(a) o indique une fixation en ortho par rapport à la chaîne latérale 3-aminopropoxy ;

(b) mélange de 2 diastéréomères ayant la configuration S sur l'atome de carbone en position 2 de la chaîne latérale 3-aminopropoxy ; $[\alpha]_{\text{D}}^{20} = -6,64^\circ$ (c = 1,58/MeOH) ;

(c) mélange de 2 diastéréomères ayant la configuration R sur l'atome de carbone du groupe A fixé sur l'azote ; $[\alpha]_{\text{D}}^{20} = -8,04^\circ$ (c = 1,9/MeOH) ;

(d) mélange de 2 diastéréomères ayant la configuration R de l'atome de carbone du groupe A ; $[\alpha]_{\text{D}}^{20} = 11,43^\circ$ (c = 1,0/MeOH) ;

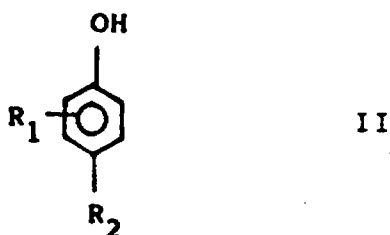


(e) mélange de 2 diastéréomères ayant la configuration R de l'atome de carbone du groupe A ; $[\alpha]_D^{20} = -7,2^\circ$ (c = 1,22/MeOH) ;

(f) mélange de 2 diastéréomères ayant la configuration R de l'atome de carbone du groupe A ; $[\alpha]_D^{20} = -7,1^\circ$ (c = 1,57/MeOH) ;

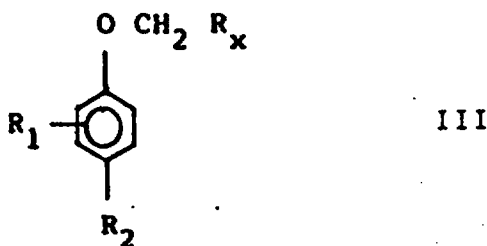
(g) mélange de 2 diastéréomères ayant la configuration R de l'atome de carbone du groupe A ; $[\alpha]_D^{20} = -7,30^\circ$ (c = 0,8/MeOH).

14. Procédé pour la préparation d'un composé de formule I, telle qu'indiquée et définie aux revendications 1 à 13, ce procédé étant caractérisé en ce qu'il comporte l'étape consistant à soumettre à une 3-amino-2-oxypropylation appropriée un composé correspondant de formule II :



dans laquelle R_1 et R_2 sont tels que définis dans l'une quelconque des revendications précédentes, ou un composé qui en est un précurseur.

15. Procédé pour la préparation d'un composé de formule I, telle que revendiquée à la revendication 1 à 13, procédé caractérisé en ce que, dans une première étape opératoire, on introduit un groupe $\text{CH}_2\text{-R}_x$, dans lequel R_x est un groupe capable de réagir avec une amine primaire pour donner un groupe 2-amino-1-hydroxyéthyle par O-alkylation en position 1, dans un composé de formule II, ce qui donne un composé correspondant de formule III :



dans laquelle R_1 et R_2 sont tels que définis dans l'une quelconque des revendications 1 à 13, et, dans une seconde étape opératoire, on amine le composé de formule III à l'aide d'un composé correspondant de formule IV :



dans laquelle A, W, X et R sont tels que définis dans l'une quelconque des revendications 1 à 13 et, lorsque cela est nécessaire, ce composé ayant au moins un groupe hydroxyle sous forme estérifiée de manière appropriée donnant un composé résultant de formule I.

16. Composition pharmaceutique, caractérisée en ce qu'elle comprend un composé selon l'une quelconque des revendications 1 à 13, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, en association avec un support, véhicule ou diluant pharmaceutiques.



17. Utilisation d'un composé tel que revendiqué dans l'une quelconque des revendications 1 à 13 pour la fabrication d'une composition destinée à servir dans un procédé de traitement du corps humain ou animal, de préférence destinée à servir au traitement prophylactique ou thérapeutique de maladies que l'on sait couramment répondre à un blocage de récepteurs β adrénergiques, comme les maladies que l'on trouve affecter le cœur, ce qui comprend de l'hypertension, un infarctus du myocarde, une surstimulation sympathique, de la migraine, du glaucome, de la thyrotoxicose, des troubles du rythme cardiaque et une défaillance du cœur.

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