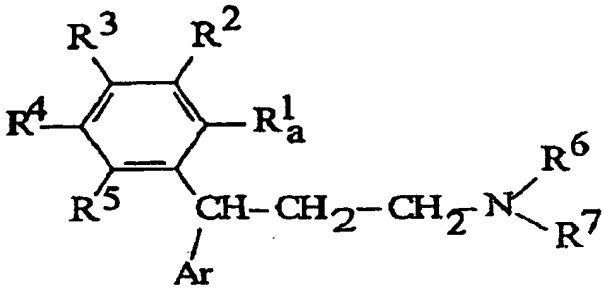
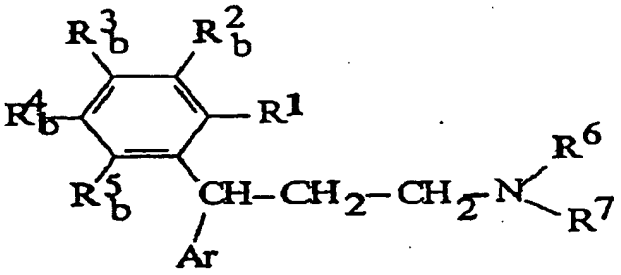


Formule VI

dans laquelle R^2 à R^7 et Ar sont tels que définis dans la revendication 1, et R^1a est carboxyl ou alkoxy, la conversion de R^1a en hydroxy, ou

f) dans un composé de Formule VII

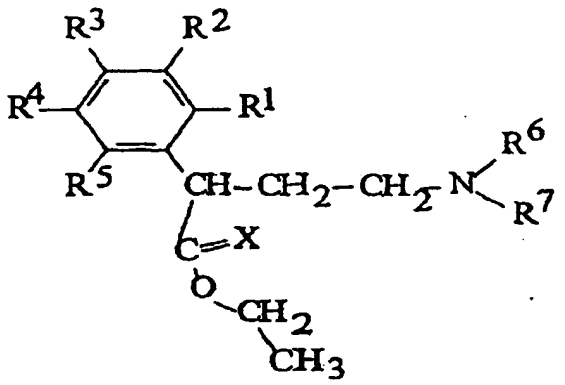


Formule VII

dans laquelle R^1, R^6, R^7 et Ar sont tels que définis dans la revendication 1, et un des éléments R^2b à R^5b est alkylène et les autres sont tels que définis dans la revendication 1 pour R^2 à R^5, la réduction de l'alkylène en alkyle, hydroxyalkyle ou dihydroxyalkyle, ou

g) dans un composé de Formule I tel que défini dans la revendication 1, la conversion d'un ou plusieurs des groupes R^1 à R^5 en un autre groupe ou en d'autres groupes R^1 à R^5, ou

h) la réaction d'un composé de Formule VIII

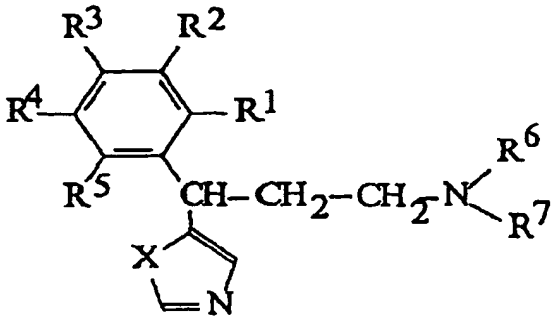


Formule VIII

dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, et X est oxygène ou soufre, avec un composé de Formule IX

$CH_3N{=}C$: formule IX

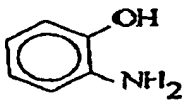
pour former un composé de Formule Ia



Formule Ia

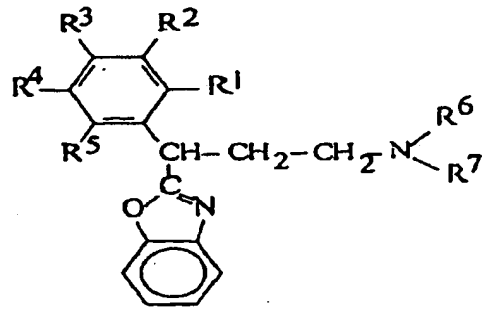
dans laquelle R^1 à R^7 et X sont tels que définis ci-dessus, ou

i) la réaction d'un composé de Formule VIII défini ci-dessus, dans lequel X est oxygène, avec un composé de Formule X



Formule X

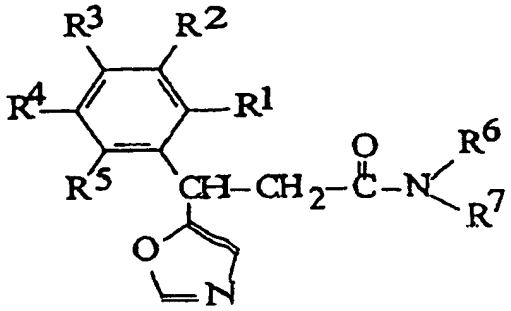
pour former un composé de Formule Ib



Formule Ib

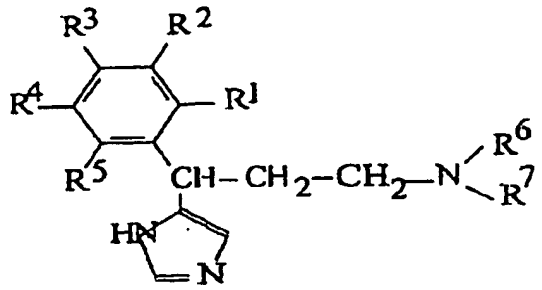
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, ou

j) la conversion d'un composé de Formule XI



Formule XI

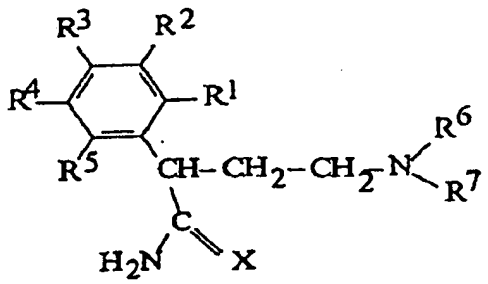
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, en un composé de Formule XII



Formule XII

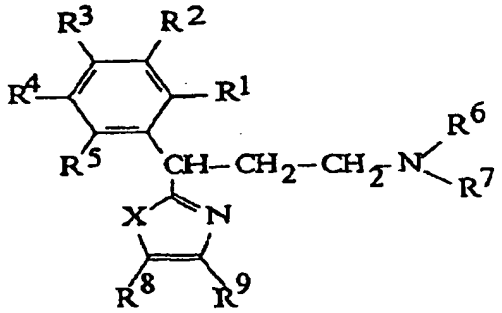
dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, ou

k) la conversion d'un composé de Formule XIII



Formule XIII

dans laquelle R^1 à R^7 sont tels que définis dans la revendication 1, et X est oxygène ou soufre, en un composé de Formule XIV



Formule XIV

dans laquelle R^1 à R^7 et X sont tels que définis ci-dessus, et R^8 et R^9 sont indépendamment hydrogène ou alkyl, et

(i) si nécessaire, la séparation des groupes de protection des éléments hydroxy dans les composés obtenus,
(ii) si désiré, la conversion des bases de Formule I obtenues en leurs sels avec des acides physiologiquement acceptables, ou vice versa, et/ou
(iii) si désiré, la séparation d'un mélange obtenu d'isomères optiques en énantiomères individuels.

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(54) **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**

3,3-DIPHENYLPROPYLAMINDERIVATE

NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES

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(56) References cited:
WO-A-89/06644 **WO-A-94/11337**

- **LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application**

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Description

[0001] The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

[0002] In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

[0003] Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

[0004] Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

[0005] A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

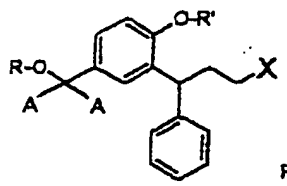
[0006] WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0007] However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

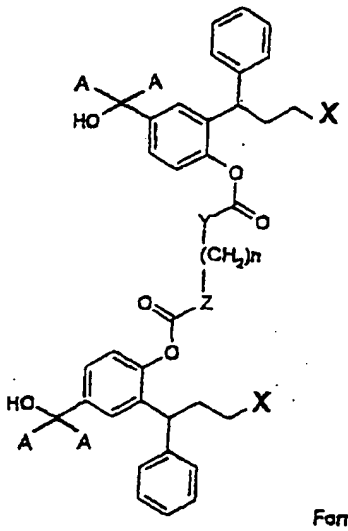
[0008] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

[0009] A further object of the invention is to provide novel prodrugs of antimuscarinic agencs with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

[0010] According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII'



Formula I



Formula VII'

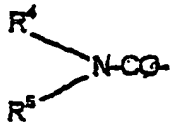
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

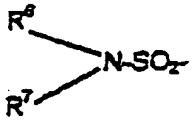
c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)



wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)

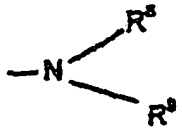


wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,
X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,
A represents hydrogen (^1H) or deuterium (^2H),
n is 0 to 12
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

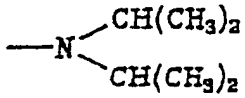
[0011] The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride and hydrobromide.

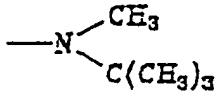
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

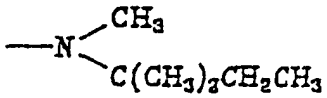
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

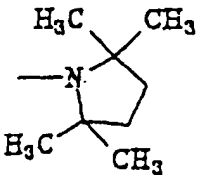
[0014] According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

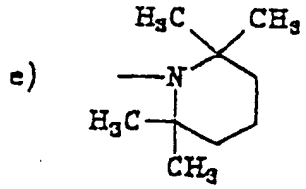
[0015] Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

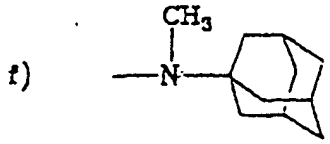
a) 

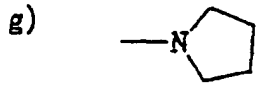
b) 

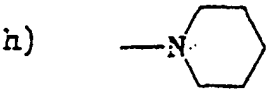
c) 

d) 









Group a) is particularly preferred.

[0016] The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

[0017] In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

[0018] The term "substituted or unsubstituted benzyl" denotes a benyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen and nitro. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

[0019] In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

[0020] The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-) and anthryl- ($C_{14}H_9$-). Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

[0021] The term "benzoyl" denotes an acyl group of the formula $-CO-C_6H_5$ wherein the phenyl ring may have one or more substituents.

[0022] Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

[0023] The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)-wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

[0024] The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

[0025] The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

[0026] The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and corresponding carbohydrate groups are, for example, described in Aspinal. The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

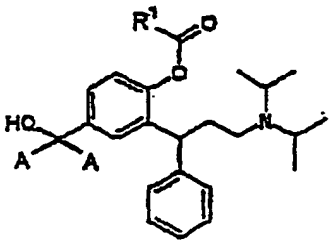
[0027] The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates and imidazolides.

[0028] The term "Bn" as used herein denotes a benzyl group.

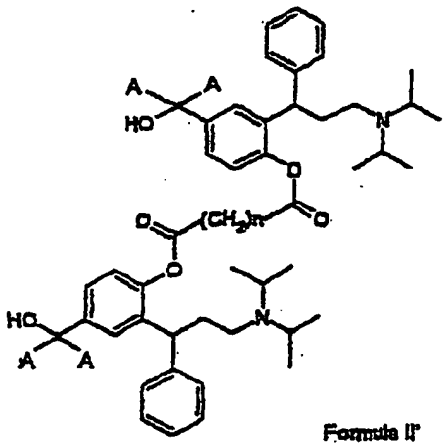
[0029] Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

[0030] Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



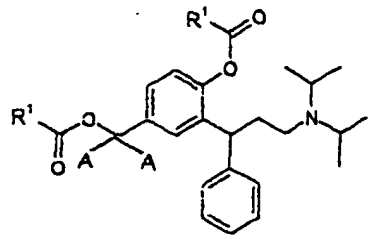
Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclopentanecarboxylic acid 2-(3-diisoprcpylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis- [2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



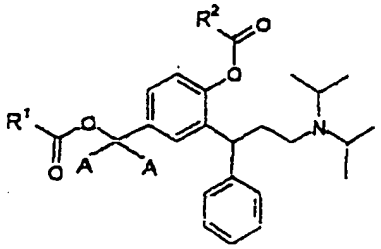
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



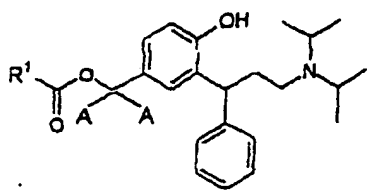
Formula IV

wherein R^1 is as defined above
and
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl
with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



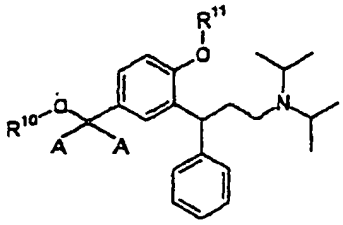
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3- (3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

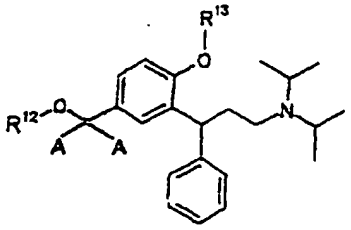
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

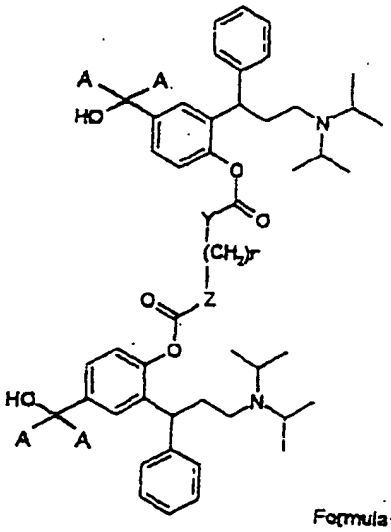
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(+) -2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±) -2- (3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert. -butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

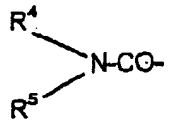


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

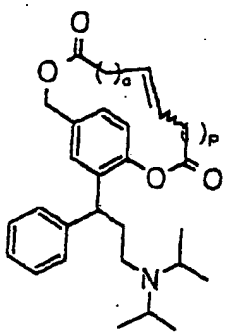
Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4- [2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic ac-

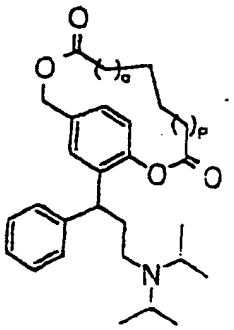
id 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



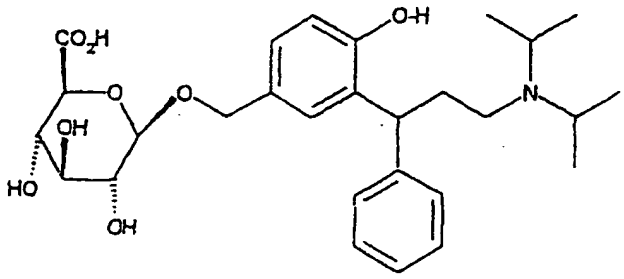
Formula IX'

wherein o and p are the same or different and represent the number of methylene units { CH_2 } and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylaminophenylpropyl)-4-hydroxymethyl-phenol

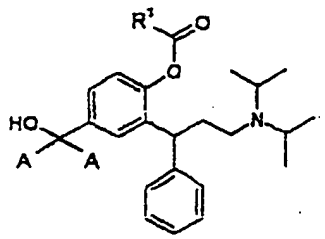
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

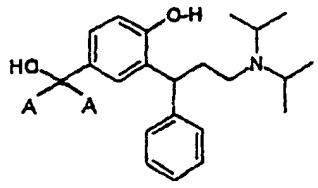
[0031] The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

[0032] A process for the production of phenolic monoesters represented by the general formula II

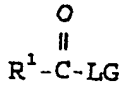


Formula II

as defined above, which comprises treatment of a compound of the formula

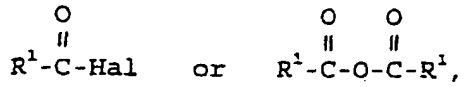


with an equivalent of an acylating agent selected from



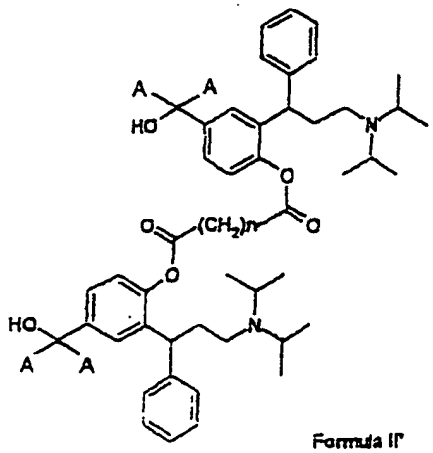
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

[0033] Preferably, the acylating agent is selected from



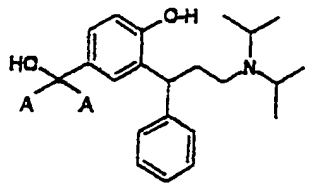
wherein Hal represents a halogen atom, preferably a chlorine. atom, and R^1 is as defined above.

[0034] A process for the production of phenolic monoesters represented by the general formula II'

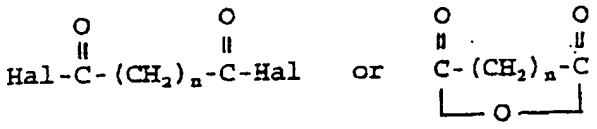


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

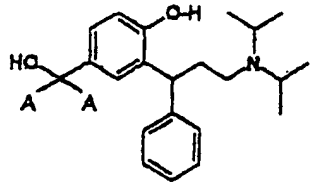


with an acylating agent selected from



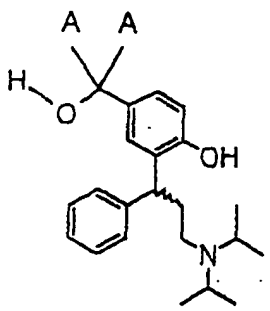
wherein Hal represents a halogen atom, preferably a chlorine atom.

[0035] Hence, in these processes, an Intermediate B having the formula

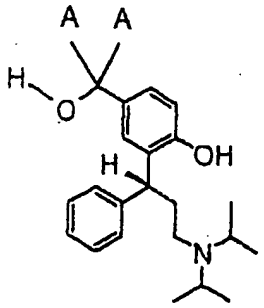


is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

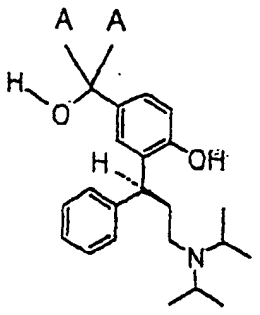
[0036] The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



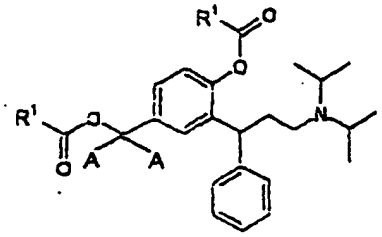
Intermediate R-(+)



Intermediate S-(-)

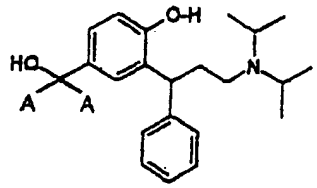
[0037] Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

[0038] The identical diesters represented by the general formula III



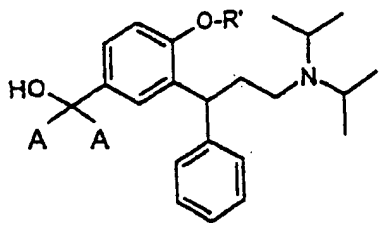
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



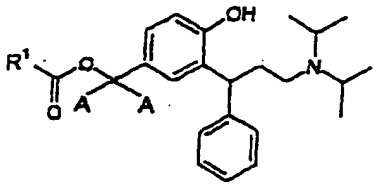
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

[0039] Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



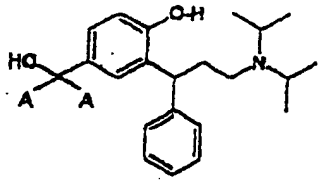
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

[0040] Benzylic monoesters represented by the general formula V



Formula V

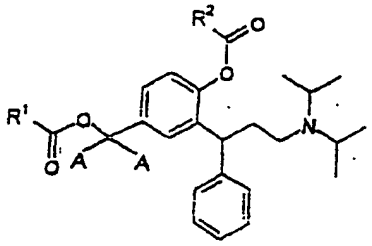
wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula



at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

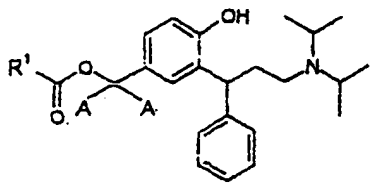
[0041] Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

[0042] The mixed diesters represented by the general formula IV



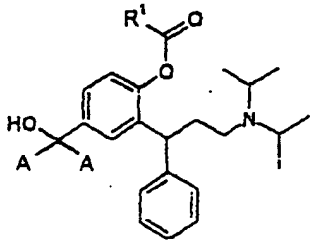
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

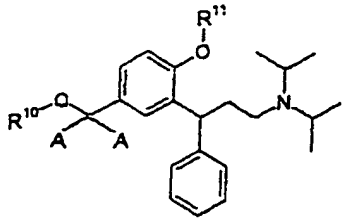


Formula II

as defined hereinbefore.

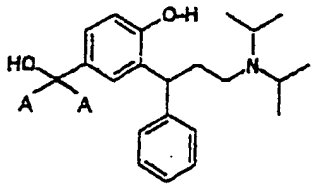
[0043] In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

[0044] Ethers represented by the general formula VI



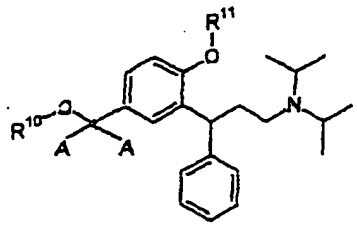
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



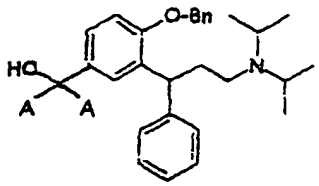
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

[0045] A further process for the preparation of ethers represented by the general formula VI

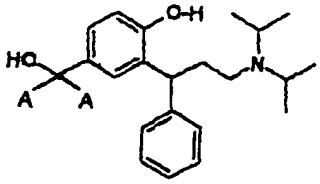


Formula VI

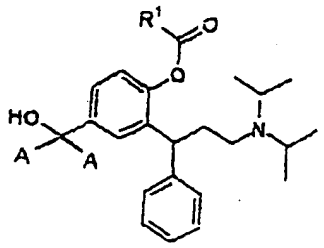
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

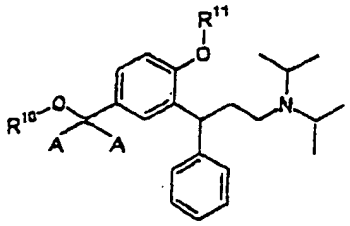


and



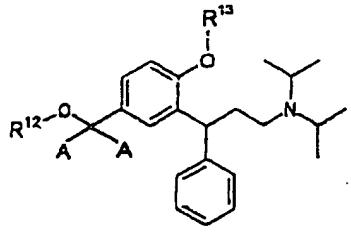
Formula II

or



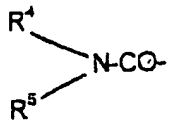
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or

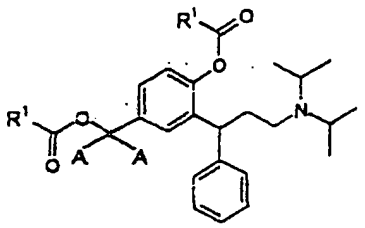


Formula VII

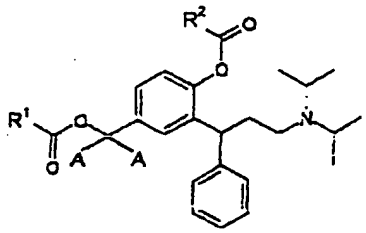
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



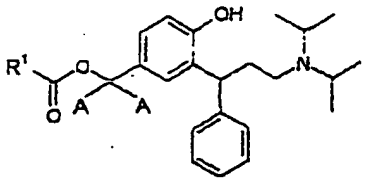
wherein R^4 and R^5 are as defined above
or of benzylic acylates selected from



Formula III



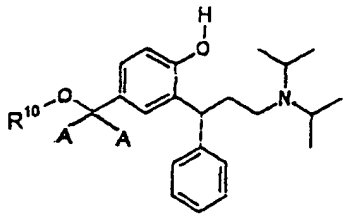
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

[0046] Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

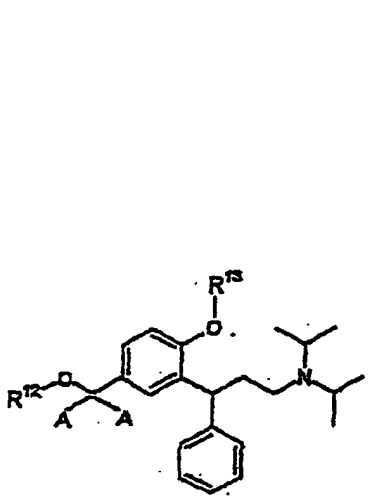


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

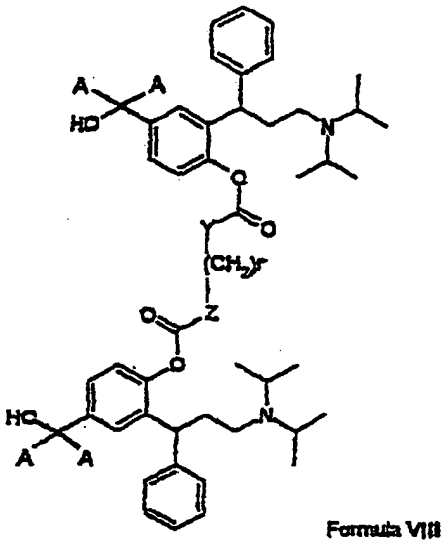
[0047] In summary, regioselective modification of the *benzylic hydroxy groups is* achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

[0048] Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

[0049] Carbonates and carbamates represented by the general formulae VII and VIII

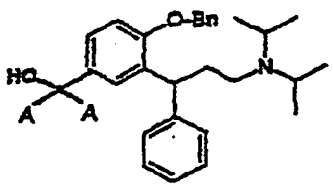


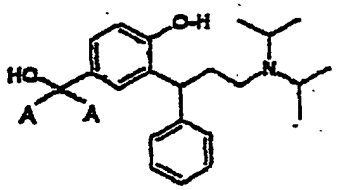
Formula VII

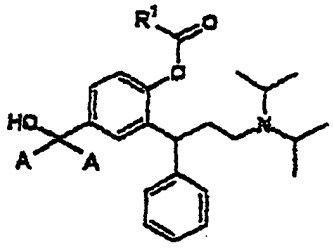


Formula VIII

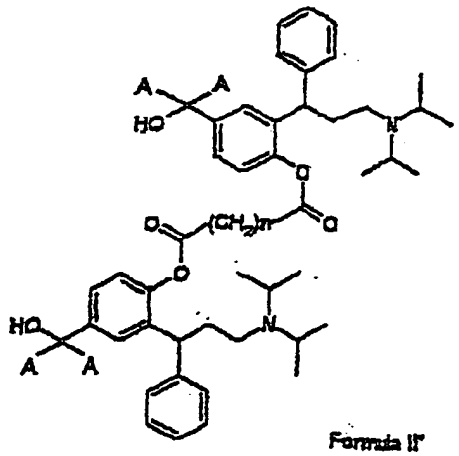
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



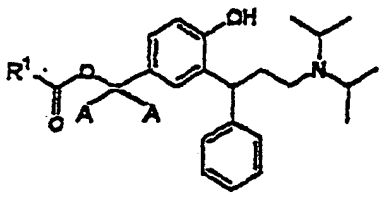




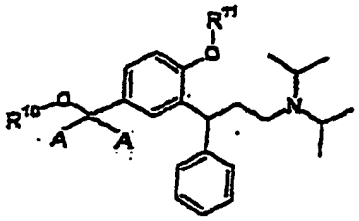
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined above with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

[0050] The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents -C(=O)-Y-R^3, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

[0051] The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

[0052] They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

[0053] The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection or for nasal spray administration, in accordance with accepted pharmceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum and colloidal silicon dioxide. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents and buffers.

[0054] The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups and elixirs in the form of sterile solutions, suspensions or emulsions for parenteral administration.

[0055] The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

[0056] The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

[0057] The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

[0058] All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^1H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

[0059] Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.

Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%) ; (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%) ; (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).

Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.

Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.

IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.

Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives. Combined liquid chromatography-mass spectrometry (LC-MS) :

Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

[0060] An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR ($CDCl_3$) : 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

[0061] A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with echylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one,* m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$) : 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

[0062] A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$) : 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0063] A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid methyl ester* (0,391 g, 0,92 mmol)

in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid,* colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$) : 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, M^+), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr) : 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

[0064] Alternatively, the crude reaction mixture from the above described synthesis of *(±) -3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0065] Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid* (815.6 g, 1.85 mol) and 1S, 2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2- benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$) : 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

[0066] 1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

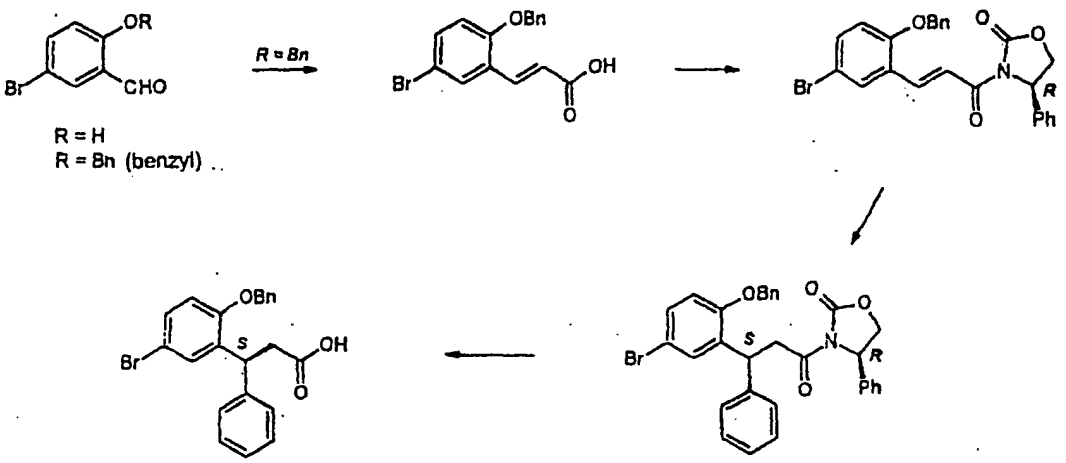
S-(+)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionic acid

[0067] The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was re-dissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$) : 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

[0068] *S- (+)-3- (2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0069]



2-Benzyloxy-5-bromobenzaldehyde

[0070] To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromobenzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

[0071] A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one

[0072] Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3- [3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

[0073] To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3- [3- (2-Benzyloxy-5-bromophenyl)-acryloyl] -(4R)-4-phenyloxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

[0074] A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl) - (3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

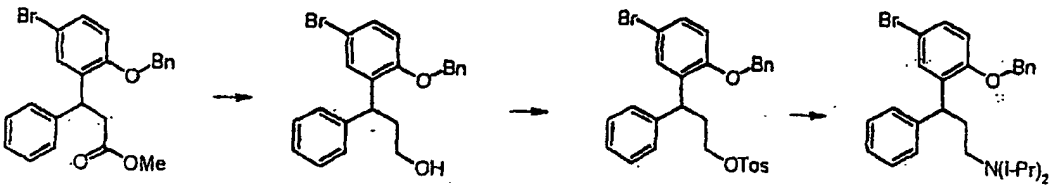
[0075] HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

[0076] **R-(-)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionic acid** Conjugate organocuprate addition of phenylmagnesiumbromide to-*3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzylcxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystallizations, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route

[0077]



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

[0078] A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, (±)-3-*(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol.* NMR ($CDCl_3$) : 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

[0079] The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

[0080] A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$) : 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16,

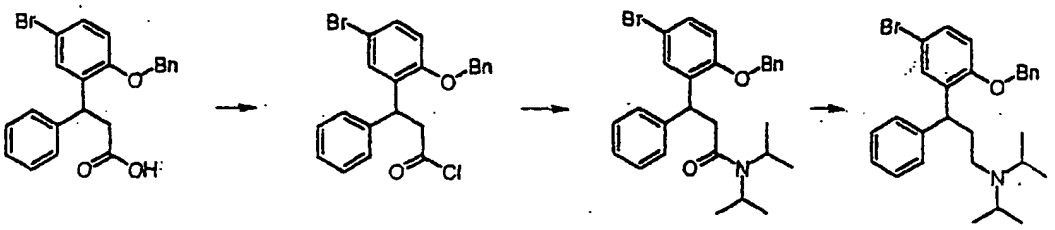
155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0081] A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9% yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route

[0082]



S-(+)-3-(2-Benzyloxy-5-bromophenyl) -3-phenylpropionyl chloride

[0083] Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 9). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

[0084] A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temperature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3- (2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

[0085] The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0086] To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tecrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent

was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%). of the title compound as a viscous colourless oil, tlc: (4) 0.86. The NMR spectrum corresponds to the product, obtained from the tosylate precursor (see above).

S-(+)-[3- (2-Benzyloxy-5-bromophenyl)-3-phenylpropyl] -diisopropylamine

[0087] Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

[0088] Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

[0089] The optical purities were determined by chiral HPLC using Chiralpak OD columns.

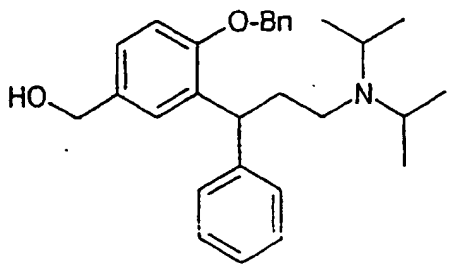
(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

[0090] An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD) : 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±) - [4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

[0091] The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$) : 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl] - [C^2H]methanol

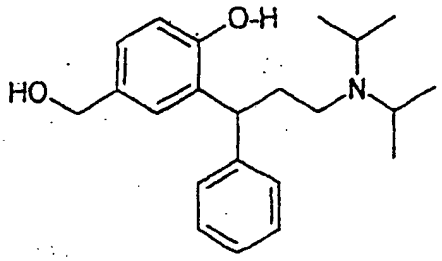
Intermediate d_2-A (n = 2)

[0092] Repetition of the above described reduction of the methylester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$) : 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03,128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Intermediate B (n = 1)

[0093] A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-di-isopropylamino-1-phenylpropyl)-4-hydroxymethylphenol,* m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$) : 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.
Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0094] *Hydrogenolysis of S-(-)-[4-benzyloxy-3- (3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S- (+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$) : 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.
S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6) : 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

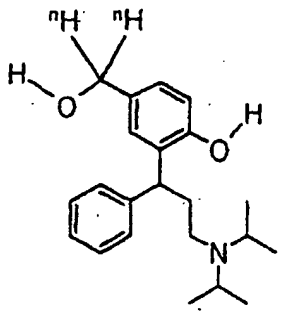
[0095] Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).
R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water) ; NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.
S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B (n = 2)

[0096] A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave
(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl] - [$^2H_2$]methanol
as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$) : 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137,17, 144.30. 155.52.

[0097] A solution of the above (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc : (4) 0.57 (starting material 0.77). NMR ($CDCl_3$) : 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



Intermediate d_2-B

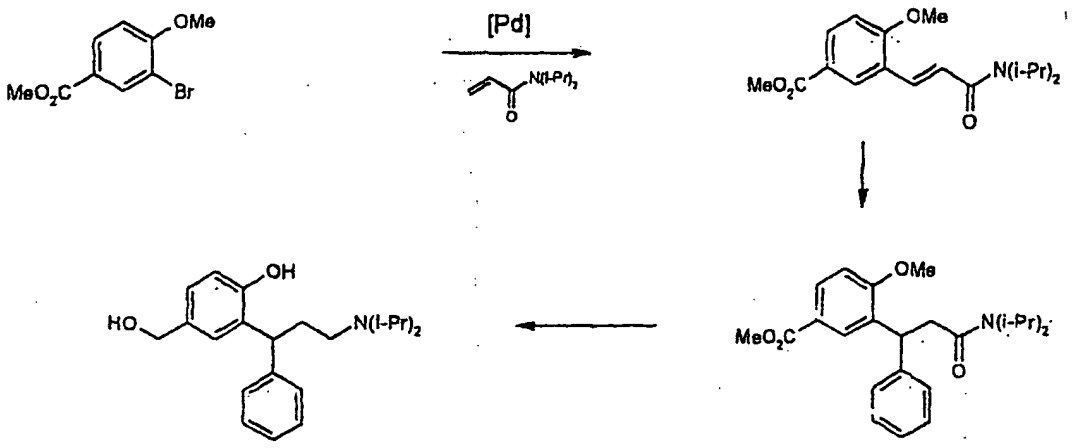
n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$] methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B

[0098]



Intermediate B

N,N-Diisopropyl-acrylamide

[0099] A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$) : 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

[0100] The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.
A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40. NMR (CD_2Cl_2) : 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07. MS (EI, DI, 105°C) : 319 (M^+, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxybenzoic acid methyl ester)

[0101] The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.
A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclohexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave
(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide
as a viscous slightly yellow syrup (1.8 g, 44% yield). NMR (CD_2Cl_2) : 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C) : 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0102] A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room temperature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

[0103] A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of
S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate
in 33% yield, tlc: (4) : 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD) : 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

[0104] A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol)

[0105] Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+) - (2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids

[0106] A stirred solution of (±)-*2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5,00 mmol carboxylic acid monochloride for compounds of formula II, 2.50 mmol for compounds of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

[0107] To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

[0108] A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

[0109] The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4 hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4) ; NMR ($CDCl_3$) : 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$) : 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$) : 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1) ; NMR ($CDCl_3$) : 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD) : 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$) : 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$) : 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%) ;gradually crystallized upon refrigeration; NMR ($CDCl_3$) : 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70. 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 154.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl-)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4) ; colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform) ;
NMR ($CDCl_3$) : 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81; 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24 ; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$) : 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$) : 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc : (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$) : 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%),

223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$) : 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 (M^+, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$) : 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 (M^+, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$) : 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 (M^+ 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$) : 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 (M^+, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$) : 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 (M^+, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$) : 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 (M^+, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$) : 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 (M^+, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD) : 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$) : 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$) : 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$) : 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

[0110] *(±)*-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triechylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

[0111] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta 37:* 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia) : 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative) : 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$) - 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc : R_f 0.82 (4) ; NMR ($CDCl_3$) : 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid *4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,* tlc: R_f 0.86 (4); NMR ($CDCl_3$) : 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; GC-MS/P-CI (ammonia) : 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$) : 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4) ; NMR ($CDCl_3$) : 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4) ; NMR ($CDCl_3$) : 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1- phenylpropyl)-phenyl ester
Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR ($DMSO-d_6$) : 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed diesters

[0112] Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters.

Working up and physical properties corresponded to the bases and salts described above.

[0113] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4 formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$) : 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4) ; NMR ($CDCl_3$) : 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$) : identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4- acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$) : 17.14, 18.53, 21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$) : 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.29, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$) : 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4) ; NMR ($CDCl_3$) : 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4) ; NMR ($CDCl_3$) : 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

[0114] A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

[0115] In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4 hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$) : 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2) ; NMR ($CDCl_3$) : 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2) ; NMR ($CDCl_3$) :

19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

[0116] A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

[0117] Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

[0118] Molar equivalents of bases of formula VI (R^{11} = H) , dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

[0119] In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl phenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m.p. 161°C; NMR (CD_3OD) : 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 12.9.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative) : 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD) : 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol, NMR ($CDCl_3$) : 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M\text{-}HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$) : 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$) : 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$) : 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$) : 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$) : 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$) : 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$) : 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$) : -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$) : -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±) - {3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine, tlc: R_f 0.94 (3) ; GC-MS/N-CI (methane) : 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$) : 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$) : 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$) : 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

[0120] A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane 20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

[0121] N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

[0122] Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.

Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

[0123] The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

[0124] In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative) : 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6) : 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$) : 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$) : 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$) : 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$) : 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72, 130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3) ; NMR ($CDCl_3$) : 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$) : 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 35.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl) -4-N,N-diethylcarbamoyloxybenzyl ester

NMR ($CDCl_3$) : 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

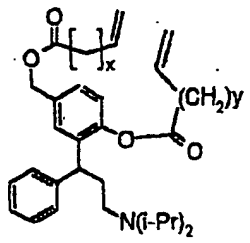
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6) ; dihydrochloride m.p. 142.5-145.6°C

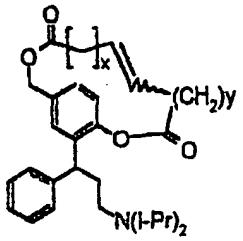
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

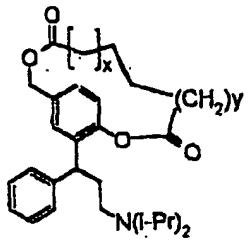
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)

[0125]







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

[0126] A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/ heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy methyl)-phenyl ester* as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$) : 18.95, 20.77, 27.75, 23.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3 -diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

[0127] Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylami-

no)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers.
NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

[0128] A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.
NMR ($CDCl_3$) : 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

[0129] All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

[0130] A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 1.5 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.
The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate 3 of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

[0131] The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

[0132] The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$) :

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm
CH resonances of the poly-lactyl chain: 5.10-5.30 ppm
CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.
Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

h) Inorganic ester

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

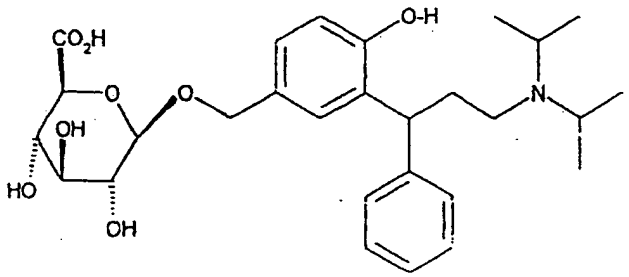
Hydrochloride

[0133] To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$) : 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl) -4-hydroxymethylphenol

((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)

[0134]



[0135] A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosylbromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester,* colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

[0136] A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,
amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

[0137] A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

[0138] The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

[0139] In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

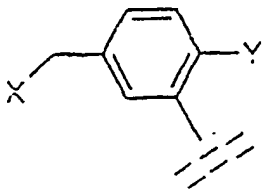
[0140] The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

[0141] The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

[0142] They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

[0143] The prodrugs introduced in the assay show the following chemical structure:



chemical structure X-/-Y		
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
ACO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

[0144] The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

[0145] The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate

to produce the corresponding carboxylic acid.

[0146] The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

[0147] These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

[0148] WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 µM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro	
Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

[0149] These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

[0150] The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 µM) concractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro	
Prodrug	IC_{50} [nM]
(+) HO-/-OH	20
(-) HO-/-OH	680
(+) HO-/-OiBut	57
(+) HO-/-OBz	180
(+) BzO-/-OBz	220
(+) AcO-/-OiBut	240

[0151] These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

[0152] Different compounds of the invention were tested for their ability to penetrate the human skin (200 µm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV detection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin	
Prodrug	Flux rate [µg/cm²/24hrs]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

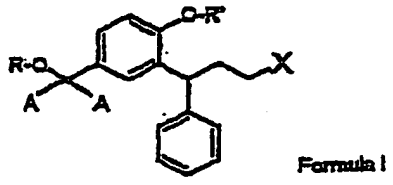
[0153] Disubsticution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

[0154] Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

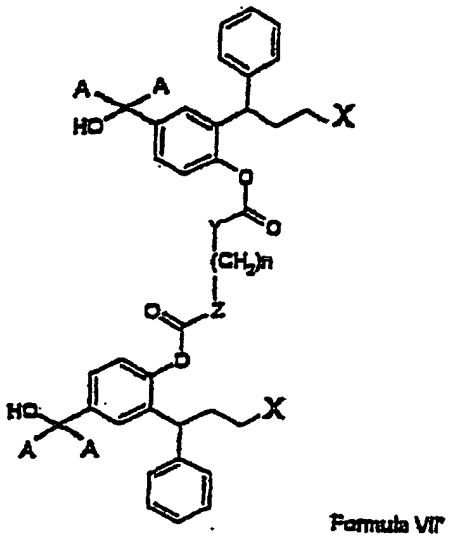
[0155] Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



Formula VII'

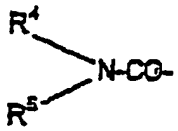
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

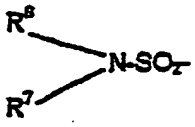
c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)



wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)

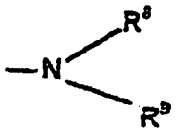


wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

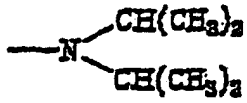
with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,
X represents a tertiary amino group of formula Ia



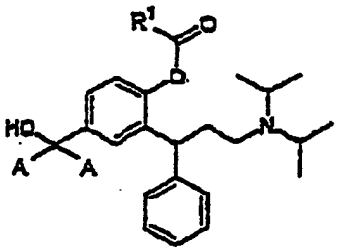
Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,
A represents hydrogen (^1H) or deuterium (^2H),
n is 0 to 12
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

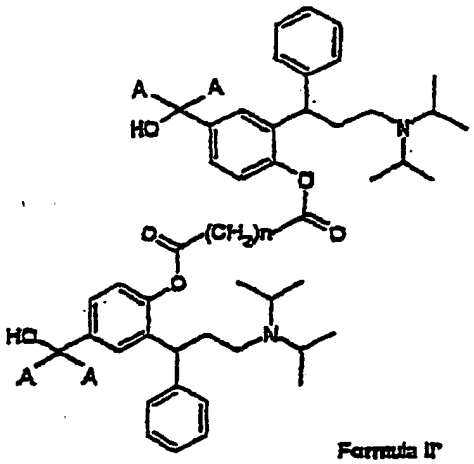
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

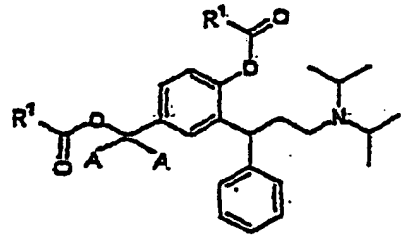
wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from :

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclopentanecarboxylic acid 2-(3-diisopronylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



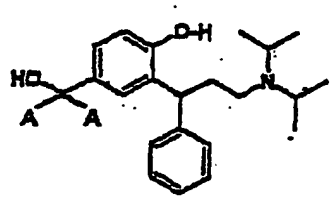
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:

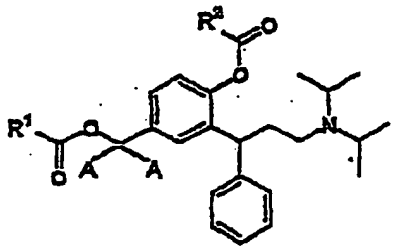
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula



wherein A is as defined in claim 1.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



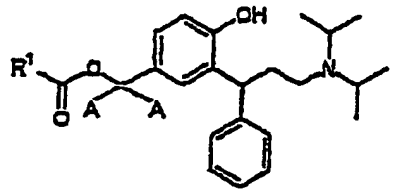
Formula IV

wherein R^1 is defined as in claim 3
and
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl
with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



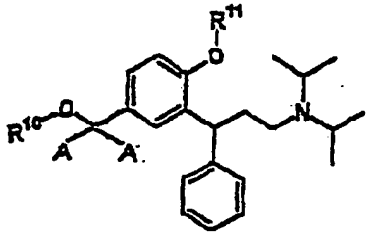
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



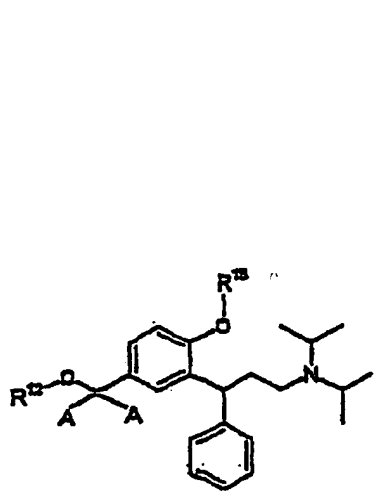
Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or -$SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

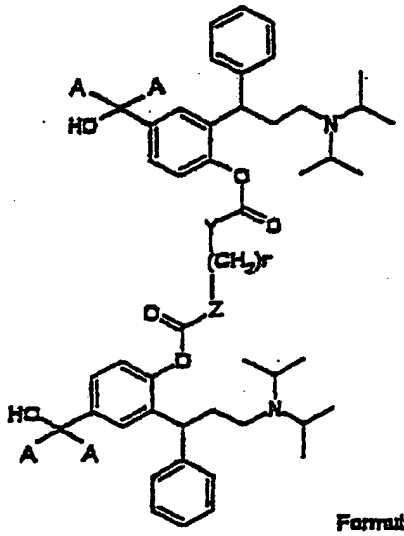
12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±) - [3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

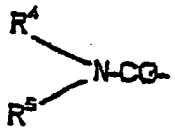


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



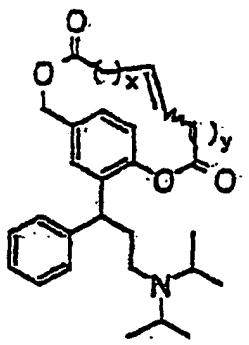
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:

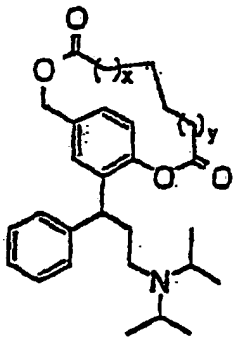
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2- (3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±) - [2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3- (3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl) -4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



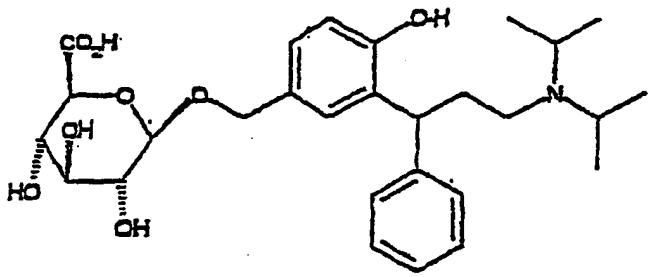
Formula IX'

wherein x and y are the same or different and represent the number of methylene units { CH_2 } and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

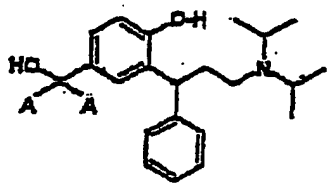


(v) (±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

(vi) cyclic oct-4-ene-1,8-dioate of Intermediate B,

(vii) cyclic octane-1,8-dioate of Intermediate B,

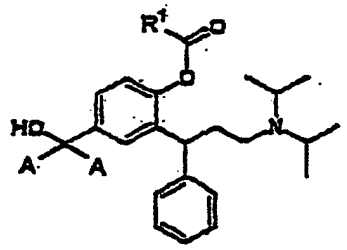
said Intermediate B having the formula



wherein A is as defined in claim 1

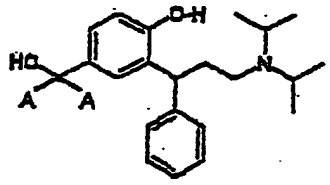
and
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

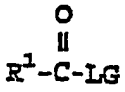


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

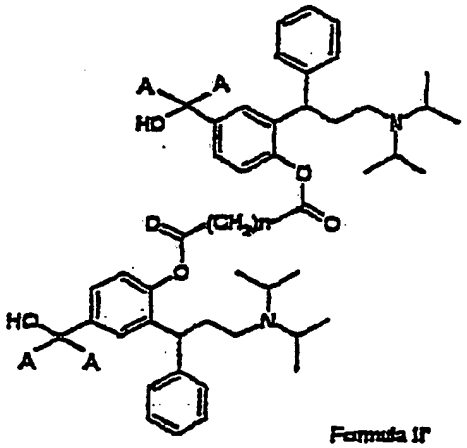


with an equivalent of an acylating agent selected from



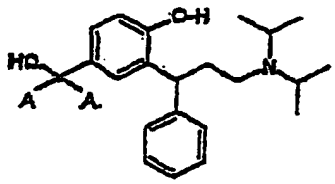
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

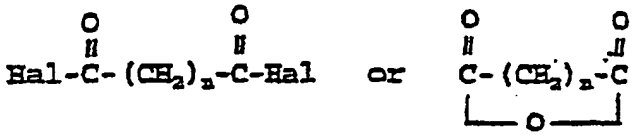


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

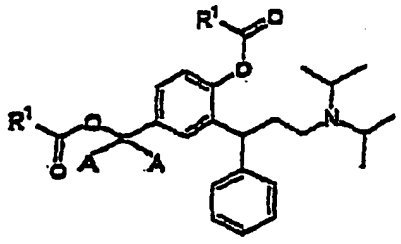


with an acylating agent selected from



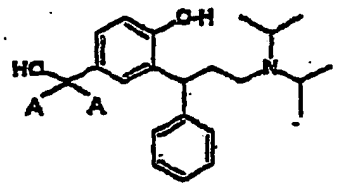
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



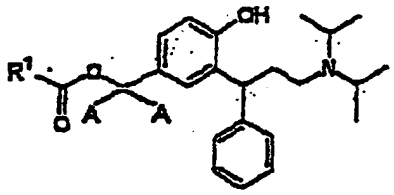
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



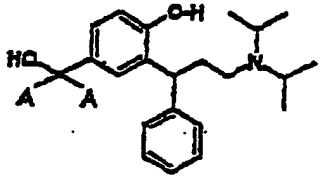
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



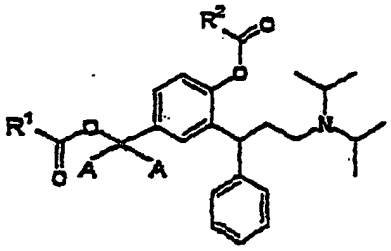
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



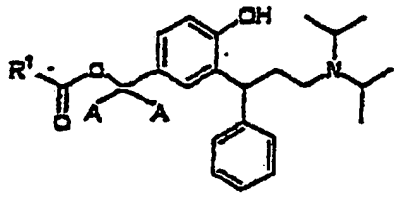
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

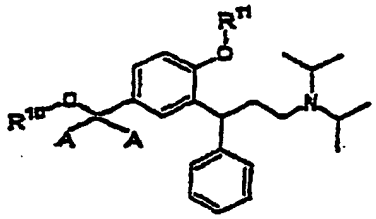
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

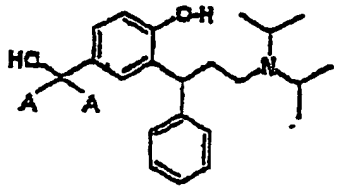
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



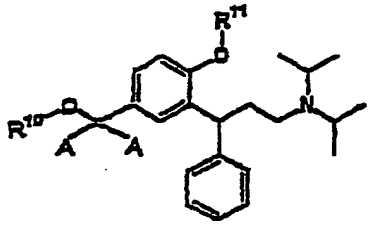
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



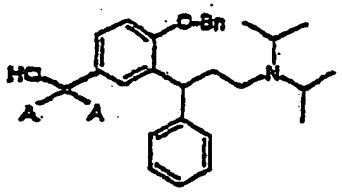
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

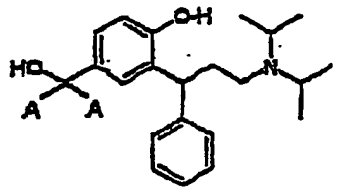


Formula VI

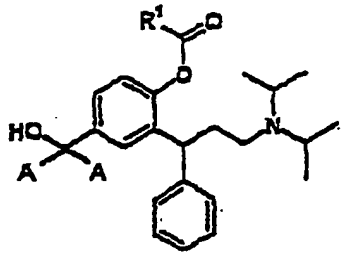
wherein R^{10} and R^{31} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

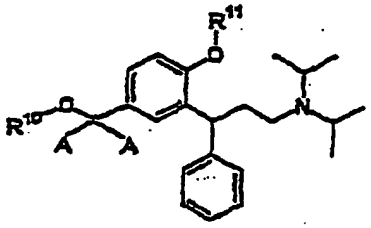


and



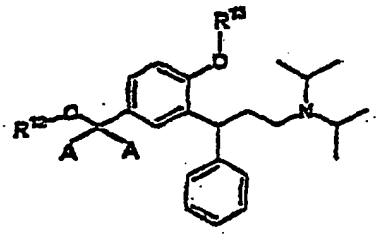
Formula II

or



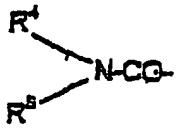
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined in claim 11 or

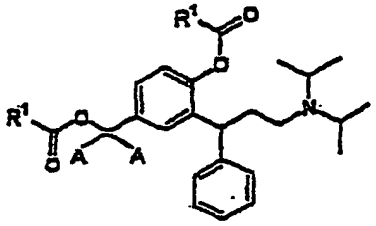


Formula VII

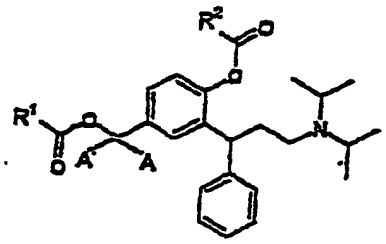
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



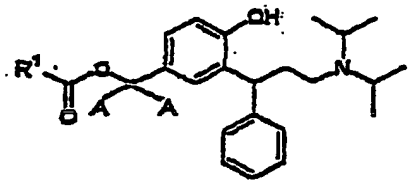
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



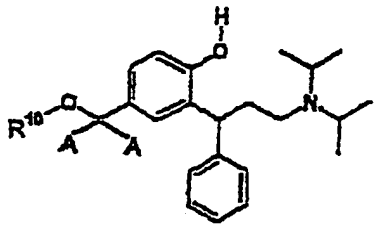
Formula IV



Formula V

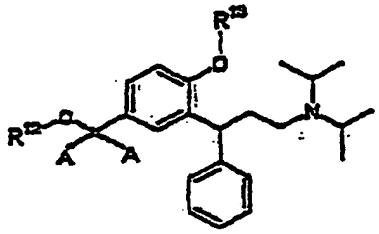
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

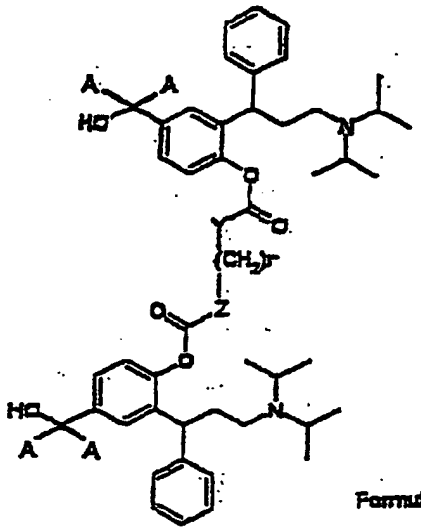


with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

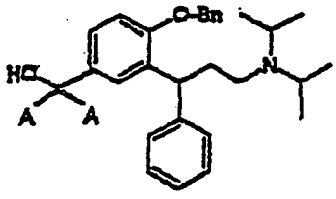


Formula VII

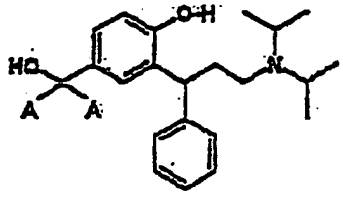


Formula VIII

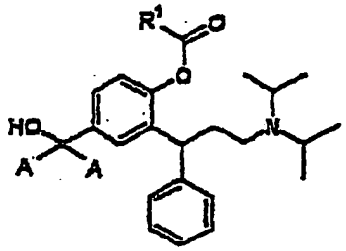
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



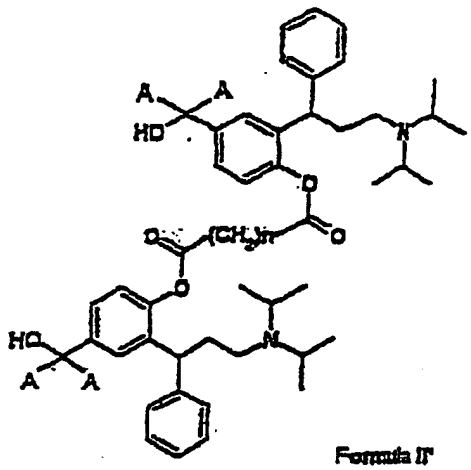
Intermediate A



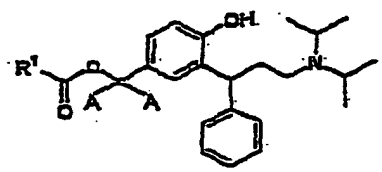
Intermediate B



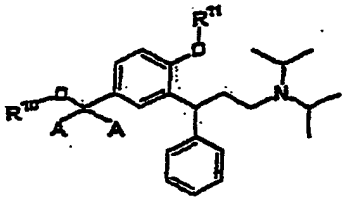
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

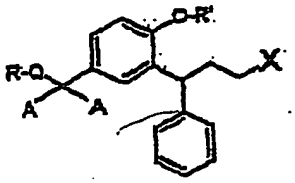
26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. A pharmaceutical composition as claimed in claim 26 which is a patch formulation.

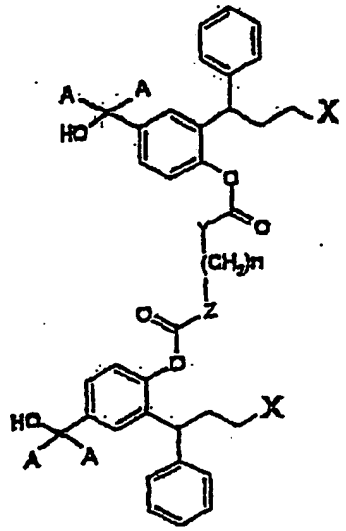
28. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

Patentansprüche

1. 3,3-Diphenylpropylamine der allgemeinen Formeln I und VII'



Formel I



Formel VII'

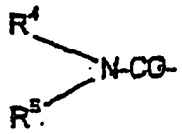
worin R und R' unabhängig ausgewählt sind aus

a) Wasserstoff, C_1-C_6-Alkyl, C_3-C_{10}-Cycloalkyl, substituiertem oder unsubstituiertem Benzyl, Allyl oder Kohlenhydrat; oder

b) Formyl, C_1-C_6-Alkylcarbonyl, Cycloalkylcarbonyl, substituiertem oder unsubstituiertem Arylcarbonyl, bevorzugt Benzoyl; oder

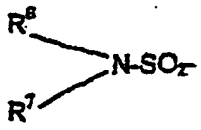
c) C_1-C_6-Alkoxycarbonyl, substituiertem oder unsubstituiertem Aryloxycarbonyl, Benzoylacyl, Benzoylglycyl, substituierten oder unsubstituierten Aminosäureresten; oder

d)



worin R^4 und R^5 unabhängig Wasserstoff, C_1-C_6-Alkyl, substituiertes oder unsubstituiertes Aryl, bevorzugt substituiertes oder unsubstituiertes Phenyl, Benzyl oder Phenoxyalkyl, worin der Alkylrest 1 bis 4 Kohlenstoffatome enthält, bedeuten und worin R^4 und R^5 zusammen mit dem Aminstickstoff einen Ring bilden können; oder

e)

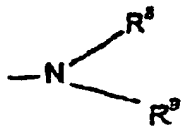


worin R^6 und R^7 unabhängig C_1-C_6-Alkyl, substituiertes oder unsubstituiertes Aryl, bevorzugt substituiertes oder unsubstituiertes Phenyl, Benzyl oder Phenoxyalkyl, worin der Alkylrest 1 bis 6 Kohlenstoffatome enthält, bedeuten; oder

f) einer Estergruppierung von anorganischen Säuren,

g) $-SiR_aR_bR_c$, worin R_a, R_b, R_c unabhängig ausgewählt sind aus C_1-C_4-Alkyl oder Aryl, bevorzugt Phenyl,

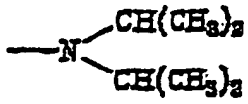
mit der Maßgabe, dass R' nicht Wasserstoff, Methyl oder Benzyl bedeutet, wenn R Wasserstoff bedeutet, R nicht Ethyl bedeutet, wenn R' Wasserstoff bedeutet,
X eine tertiäre Aminogruppe der Formel Ia



Formel Ia

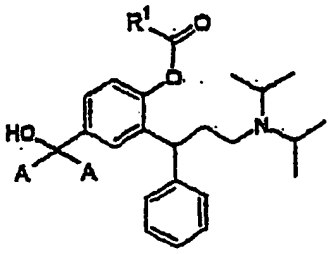
worin R^8 und R^9 nicht-aromatische Hydrocarbylgruppen, die gleich oder unterschiedlich sein können, bedeuten und die zusammen mindestens drei Kohlenstoffatome enthalten und worin R^8 und R^9 zusammen mit dem Aminstickstoff einen Ring bilden können, bedeutet,
Y und Z unabhängig eine Einfachbindung zwischen der $(CH_2)_n$-Gruppe und der Carbonylgruppe, O, S oder NH bedeuten,
A Wasserstoff (^1H) oder Deuterium (^2H) bedeutet,
n 0 bis 12 bedeutet
und
ihre Salze mit physiologisch annehmbaren Säuren, ihre freien Basen und wenn die Verbindungen in Form optischer Isomeren vorliegen, die racemischen Gemische und die individuellen Enantiomeren.

2. 3,3-Diphenylpropylamine nach Anspruch 1, worin X

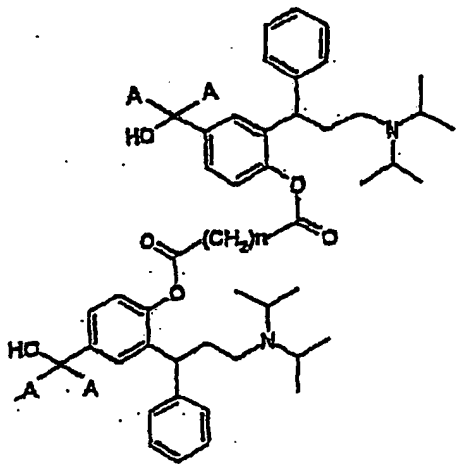


bedeutet.

3. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Phenolmonoestern, dargestellt durch die allgemeinen Formeln II und II'



Formel II



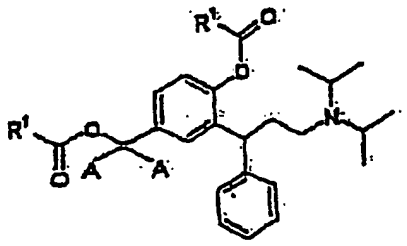
Formel II'

worin R^1 Wasserstoff, C_1-C_6-Alkyl oder Phenyl bedeutet.

4. 3,3-Diphenylpropylamine wie in Anspruch 3 beansprucht, ausgewählt aus:

(±)-Ameisensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Propionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-n-Buttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
R-(+)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2,2-Dimethylpropionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Acetamidoessigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Cyclopentancarbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Cyclohexancarbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
R-(+)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Methylbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Methylbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Acetoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-1-Naphthoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Naphthoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Chlorbenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Methoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Methoxybenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-4-Nitrobenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-2-Nitrobenzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Malonsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Bernsteinsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Pentandionsäure-bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,
(±)-Hexandionsäure-bis- [2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester.

5. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus identischen Diestern, dargestellt durch die allgemeine Formel III



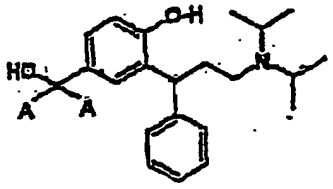
Formel III

worin R^1 die in Anspruch 3 gegebene Definition besitzt.

6. 3,3-Diphenylpropylamine nach Anspruch 5, ausgewählt aus:

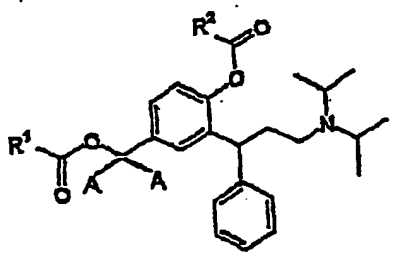
(±)-Ameisensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Essigsäure-4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Propionsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenylester,
(±)-n-Buttersäure-4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-Isobuttersäure-2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenylester,
(±)-2,2-Dimethylpropionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)benzylester,
(±)-Benzoesäure-4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
R-(+)-Henzoesäure-4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,

Poly-co-DL-Lactiden des Zwischenprodukts B, wobei das Zwischenprodukt B die Formel



besitzt, worin A die in Anspruch 1 gegebene Definition besitzt.

7. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus gemischten Diestern, dargestellt durch die allgemeine Formel IV



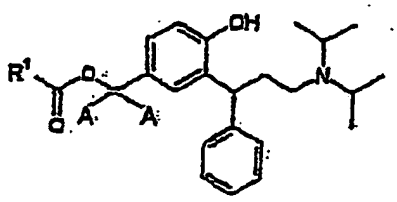
Formel IV

worin R^1 die in Anspruch 3 gegebene Definition besitzt
und
R^2 Wasserstoff, C_1-C_6-Alkyl oder Phenyl bedeutet,
mit der Maßgabe, dass R^1 und R^2 nicht identisch sind.

8. 3,3-Diphenylpropylamine nach Anspruch 7, ausgewählt aus:

(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenylester,
(±)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenylester,
R-(+)-Benzoesäure-2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenylester,
(±)-Isobuttersäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
R-(+)-Isobuttersäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-2,2-Dimethylpropionsäure-4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-2,2-dimethylpropionsäure-4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-Benzoesäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester.

9. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Benzylsäuremonoestern, dargestellt durch die allgemeine Formel V



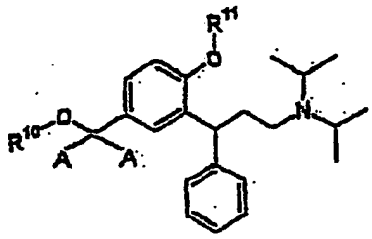
Formel V

worin R^1 die in Anspruch 3 gegebene Definition besitzt.

10. 3,3-Diphenylpropylamine nach Anspruch 9, ausgewählt aus:

(±)-Ameisensäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Essigsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Propionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Buttersäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Isobuttersäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-2,2-Dimethylpropionsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzylester,
(±)-Benzoesäure-3-(3-diisopropylamino-1-phenylpropyl)-4-hyroxybenzylester.

11. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Ethern und Silylethern, dargestellt durch die allgemeine Formel VI



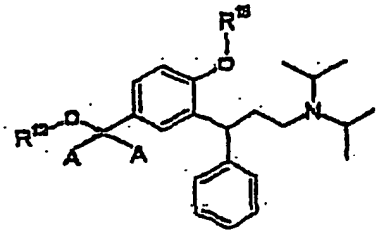
Formel VI

worin mindestens einer von R^{10} und R^{11} ausgewählt ist aus C_1-C_6-Alkyl, Benzyl oder $-SiR_aR_bR_c$, wie in Anspruch 1 definiert, und der andere von R^{10} und R^{11} zusätzlich Wasserstoff, C_1-C_6-Alkylcarbonyl oder Benzoyl bedeuten kann.

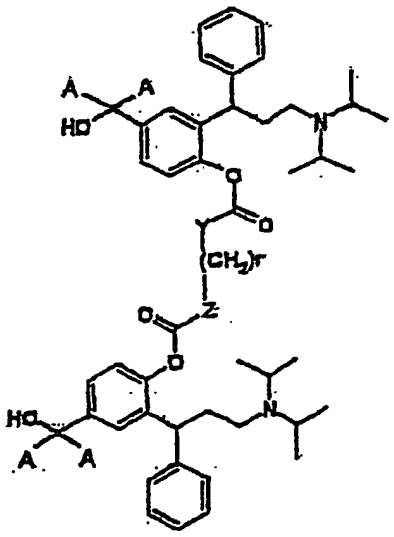
12. 3,3-Diphenylpropylamine nach Anspruch 11, ausgewählt aus:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenylester,
(±)-Essigsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenylester,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,
(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]amin,
(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol,
(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenyl]propylamin,
(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenyl]propylamin,
(±)-[4-(tert.-Butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenyl]methanol,
(±)-Essigsäure-4-(tert.-butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-4-(tert.-Butyldimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenol,
(±)-Essigsäure-4-(tert.-butyldimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-{3-[2-(tert.-Butyldimethylsilanyloxy)-5-(tert.-butyldimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}diisopropylamin,
(±)-[4-(tert.-Butyldiphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)phenyl]methanol,
(±)-Essigsäure-4-(tert.-butyldiphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenylester,
(±)-4-(tert.-Butyldiphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenol,
(±)-{3-[2-(tert.-Butyldiphenylsilanyloxy)-5-(tert.-butyldiphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}diisopropylamin,
(±)-Essigsäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Benzoesäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-Isobuttersäure-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzylester,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)phenol.

13. 3,3-Diphenylpropylamine nach Anspruch 2, ausgewählt aus Carbonaten und Carbamaten, dargestellt durch die allgemeinen Formeln VII und VIII

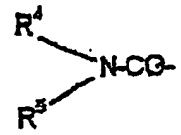


Formel VII



Formel VIII

worin Y, Z und n die in Anspruch 1 gegebenen Bedeutungen besitzen und worin R^{12} und R^{13} eine C_1-C_6-Alkoxycarbonylgruppe oder



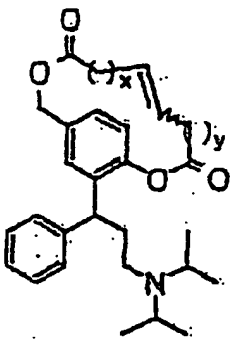
bedeuten, worin R^4 und R^5 die in Anspruch 1 gegebenen Bedeutungen besitzen.

14. 3,3-Diphenylpropylamine nach Anspruch 13, ausgewählt aus:

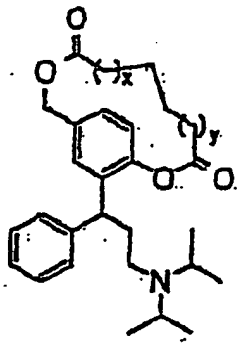
(±)-N-Ethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N,N-Dimethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N,N-Diethylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-N-Phenylcarbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]essigsäureethylesterhydrochlorid,
(±)-N-Ethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzylester,
(±)-N,N-Dimethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzylester,
(±)-N,N-Diethylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzylestern,
(±)-N-Phenylcarbaminsäure-3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzylester,
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]butyl}carbaminsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylesterethylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylesterphenylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenylesterethylester,
(±)-Carbonsäure-2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenylesterphenylester.

15. 3,3-Diphenylpropylamine, ausgewählt aus

(i) Verbindungen der Formeln IX und IX'



Formel IX



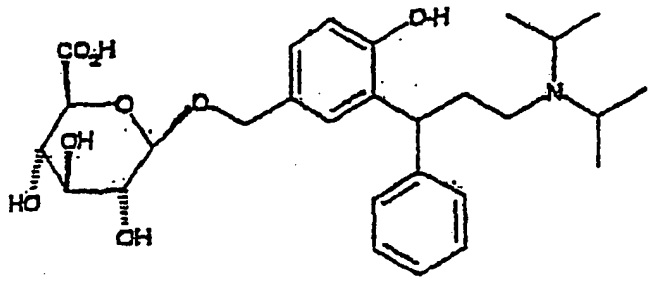
Formel IX'

worin x und y gleich oder unterschiedlich sind und die Zahl der Methyleneinheiten { CH_2 } bedeuten und im Bereich von 0 bis 6 liegen können,

(ii) (±) -Benzoesäure-2- (3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethylphenylester,

(iii) Poly-co-DL-Lactiden von 2- (3-Diisopropylaminophenylpropyl)-4-hydroxymethylphenol,

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-Dglucuronosyloxymethyl)phenol der Formel

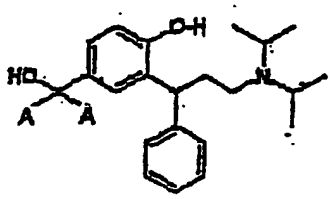


(v) (±)-Pent-4-ensäure-2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)phenylester,

(vi) cyclischem Oct-4-en-1,8-dioat des Zwischenprodukts B,

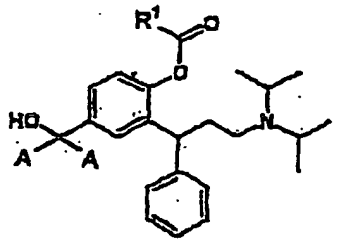
(vii) cyclischem Octan-1,8-dioat des Zwischenprodukts B,

wobei das Zwischenprodukt B die Formel



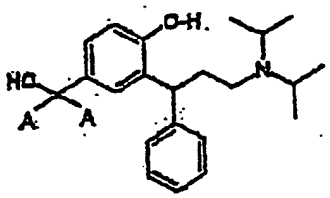
besitzt, worin A die in Anspruch 1 gegebene Definition besitzt
und
ihre Salze mit physiologisch annehmbaren Säuren, ihre freien Basen und, wenn die Verbindungen in Form optischer Isomeren vorliegen, das racemische Gemisch und die individuellen Enantiomeren.

16. Verfahren zur Herstellung von Phenolmonoestern, dargestellt durch die allgemeine Formel II

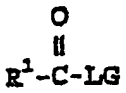


Formel II

wie in Anspruch 3 definiert, umfassend die Behandlung einer Verbindung der Formel

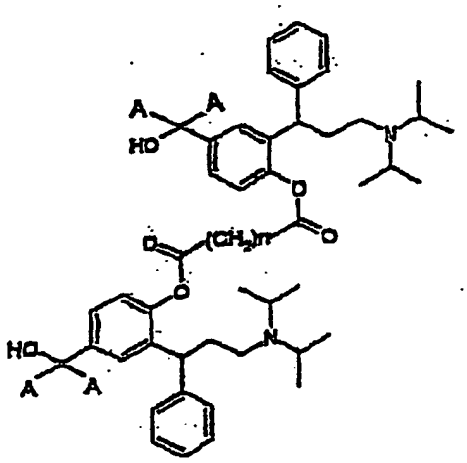


mit einem Äquivalent eines Acylierungsmittels, ausgewählt aus



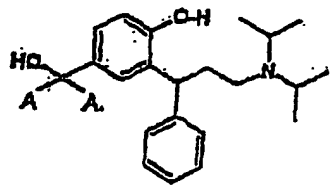
worin LG eine Austrittsgruppe, ausgewählt aus Halogenid, Carboxylat und Imidazolid, bedeutet und R^1 die in Anspruch 3 gegebenen Definitionen besitzt, in einem inerten Lösungsmittel in Anwesenheit eines Kondensationsmittels.

17. Verfahren zur Herstellung von Phenolmonoestern, dargestellt durch die allgemeine Formel II'

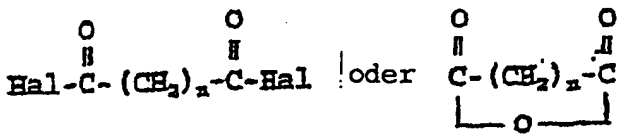


Formel II'

wie in Anspruch 3 definiert, umfassend die Behandlung von zwei Äquivalenten einer Verbindung der Formel

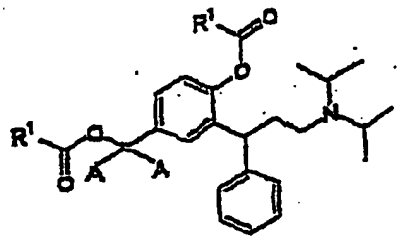


mit einem Acylierungsmittel, ausgewählt aus



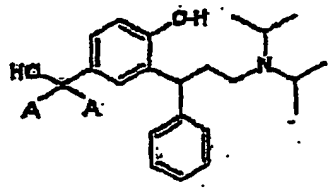
worin Hal ein Halogenatom bedeutet.

18. Verfahren zur Herstellung identischer Diester, dargestellt durch die allgemeine Formel III



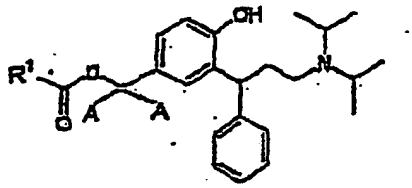
Formel III

wie in Anspruch 5 definiert, umfassend die Behandlung einer Verbindung der Formel



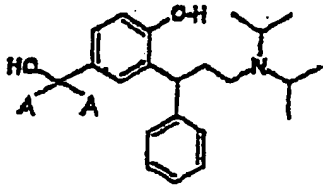
mit mindestens zwei Äquivalenten des Acylierungsmittels wie in Anspruch 16 definiert.

19. Verfahren zur Herstellung von Benzylsäuremonoestern, dargestellt durch die allgemeine Formel V



Formel V

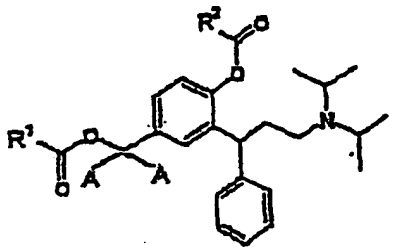
wie in Anspruch 9 definiert, umfassend die Behandlung einer Verbindung der Formel



bei Raumtemperatur und unter wasserfreien Bedingungen mit aktivierten Estern in Anwesenheit von Enzymen,

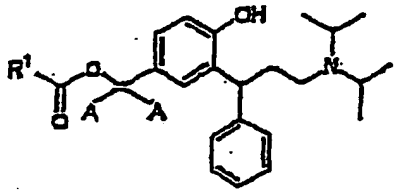
ausgewählt aus Lipasen oder Esterasen.

20. Verfahren zur Herstellung gemischter Diester, dargestellt durch die allgemeine Formel IV



Formel IV

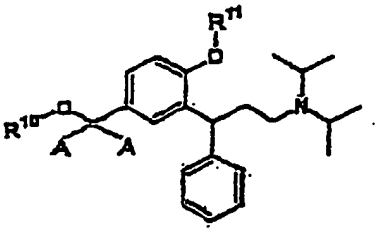
wie in Anspruch 7 definiert, umfassend die Acylierung eines Benzylsäuremonoesters, dargestellt durch die allgemeine Formel V



Formel V

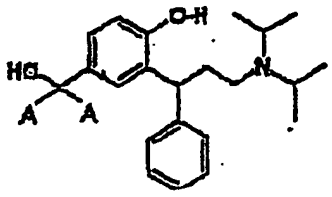
wie in Anspruch 9 definiert, oder eines Phenolmonoesters, dargestellt durch die Formel II, wie in Anspruch 3 definiert.

21. Verfahren zur Herstellung von Ethern, dargestellt durch die allgemeine Formel VI



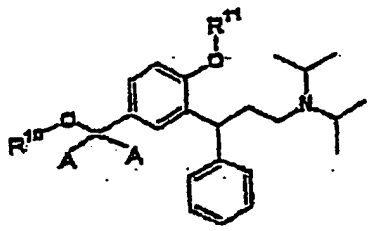
Formel VI

wie in Anspruch 11 definiert, worin R^{11} Wasserstoff bedeutet, umfassend die Umsetzung einer Verbindung der Formel



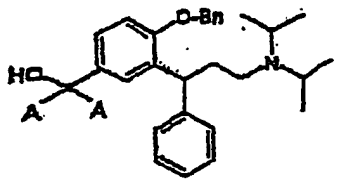
mit einem Alkohol R^{10}-OH in Anwesenheit eines Veresterungskatalysators.

22. Verfahren zur Herstellung von Ethern, dargestellt durch die allgemeine Formel VI

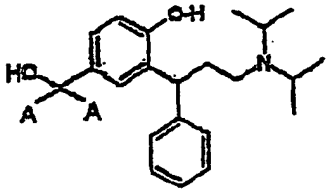


Formel VI

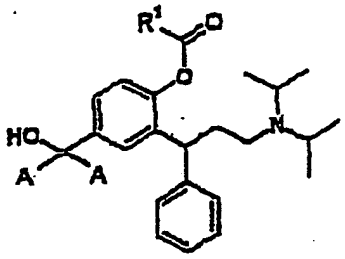
worin R^{10} und R^{11} die in Anspruch 11 gegebenen Definitionen besitzen, umfassend die Säure- oder Basenbehandlung von freien Benzylalkoholen, ausgewählt aus



und

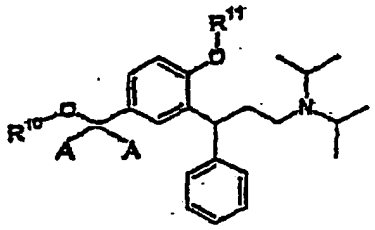


und



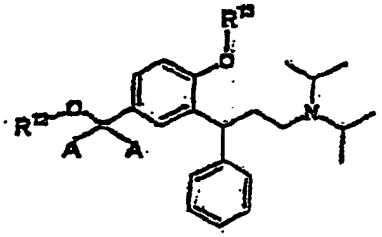
Formel II

oder



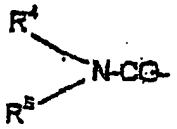
Formel VI

worin R^{10} Wasserstoff bedeutet und R^{11} die in Anspruch 11 gegebene Bedeutung besitzt, oder

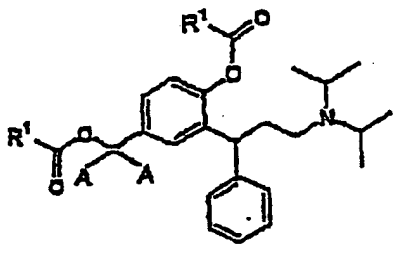


Formel VII

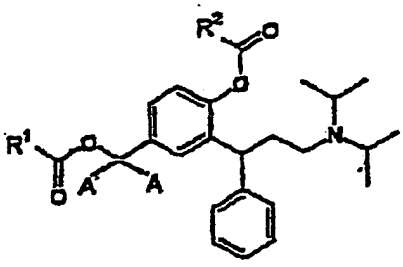
worin R^{12} Wasserstoff bedeutet und R^{13} eine C_1-C_6-Alkoxycarbonylgruppe bedeutet, oder



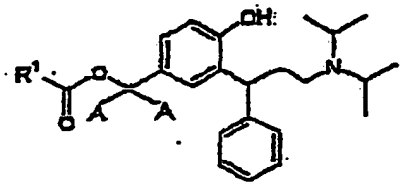
worin R^4 und R^5 die in Anspruch 1 gegebene Bedeutung besitzen, oder von benzylischen Acylaten, ausgewählt aus



Formel III



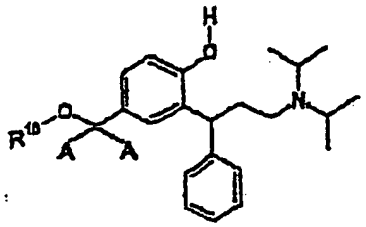
Formel IV



Formel V

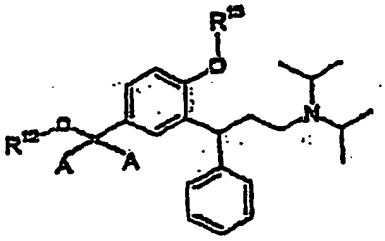
worin R^1 und R^2 die in Anspruch 7 gegebene Bedeutung besitzen, in Anwesenheit geeigneter Hydroxyreagentien.

23. Verfahren zur Herstellung von Ethern der Formel VI, wie in Anspruch 11 definiert, umfassend die Behandlung einer Verbindung der Formel

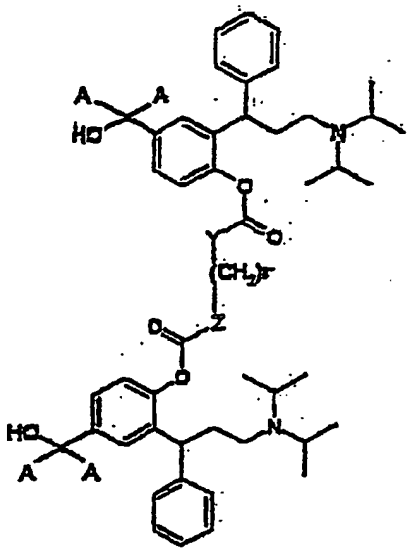


mit einem Alkylierungsmittel, ausgewählt aus Alkylhalogeniden, Alkylsulphaten und Alkyltriflaten, wobei die Alkylgruppe 1 bis 6 Kohlenstoffatome enthält.

24. Verfahren zur Herstellung von Carbonaten und Carbamaten, dargestellt durch die allgemeinen Formeln VII und VIII

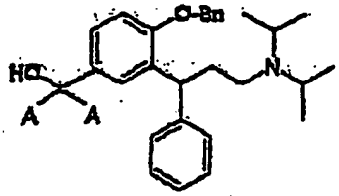


Formel VII

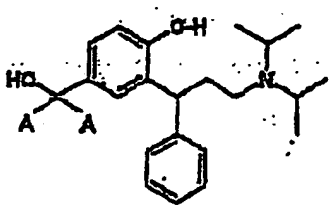


Formel VIII

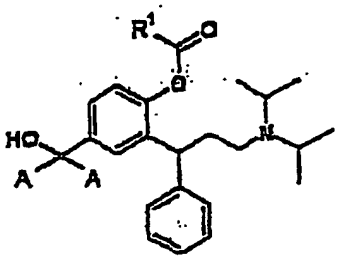
wie in Anspruch 13 definiert, umfassend die Umsetzung einer Verbindung, ausgewählt aus der Gruppe bestehend aus



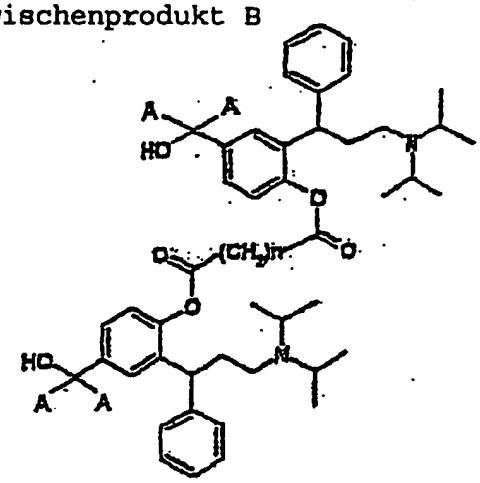
Zwischenprodukt A



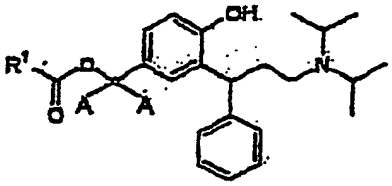
Zwischenprodukt B



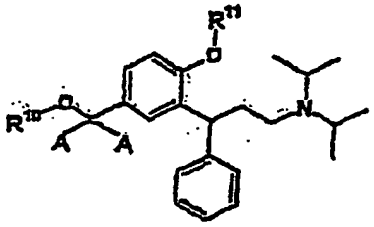
Formel II



Formel II'



Formel V



Formel VI

worin R^1 wie in Anspruch 3 definiert ist, n 0 bis 12 bedeutet, Bn Benzyl bedeutet, einer der Substituenten R^{10} oder R^{11} Wasserstoff bedeutet und der andere die in Anspruch 11 gegebene Definition besitzt, mit aktivierten Carbonylverbindungen oder Carbonyl-Vorstufereagentien, ausgewählt aus Haloformiaten, Ketenen, aktivierten Estern, gemischten Anhydriden von organischen oder anorganischen Säuren, Isocyanaten und Isothiocyanaten.

25. 3,3-Diphenylpropylamine nach den Ansprüchen 1 bis 15 für die Verwendung als pharmazeutisch aktive Substanzen, insbesondere als antimuskarinische Mittel.

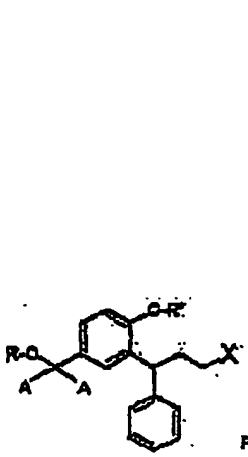
26. Pharmazeutische Zubereitung, umfassend ein 3,3-Diphenylpropylamin, wie in einem der Ansprüche 1 bis 15 definiert, und einen pharmazeutisch verträglichen Träger.

27. Pharmazeutische Zubereitung nach Anspruch 26, die eine Plättchen- bzw. Pflaster-Zubereitung ist.

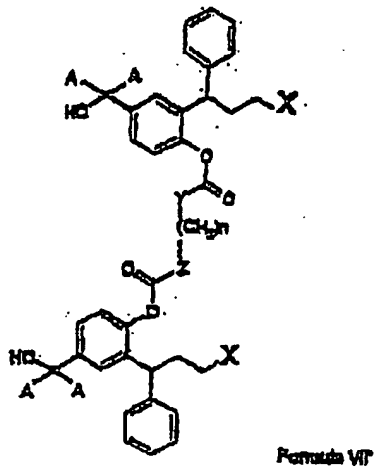
28. Verwendung von 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 15 zur Herstellung eines antimuskarinischen Arzneimittels.

Revendications

1. 3,3-Diphénylpropylamines de formules générales I et VII' :



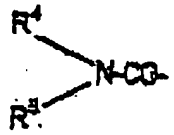
Formule I



Formule VII'

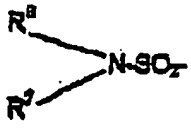
dans lesquelles R et R' sont indépendamment choisis à partir

a) d'un atome d'hydrogène, d'un groupement alkyle C_1-C_6, d'un groupement cycloalkyle C_9-C_{10}, d'un benzyle substitué ou non substitué, d'un groupement allyle ou d'un carbohydrate ; ou
b) d'un groupement formyle, d'un groupement alkylcarbonyle C_1-C_6, d'un cycloalkylcarbonyle, d'un arylcarbonyle substitué ou non substitué, de préférence le benzoyle ; ou
c) d' un groupement alkoxycarbonyle C_1-C_6, d'un aryloxycarbonyle substitué ou non substitué, d'un benzoylacyle, d'un benzoylglycyle, d'un résidu d'aminoacide substitué ou non substitué ; ou
d)



dans lequel R^4 et R^5

représentent indépendamment un atome d'hydrogène, un groupement alkyle C_1-C_6, un groupement aryle substitué ou non substitué, de préférence un phényle substitué ou non substitué, un groupement benzyle ou un phénoxyalkyle dans lequel le résidu alkyle a 1 à 4 atomes de carbone et dans lequel R^4 et R^5 peuvent former un cycle ainsi que l'azote de l'amine ; ou
e)

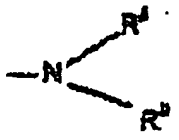


dans lequel R^6 et R^7

représentent indépendamment un groupement alkyle C_1-C_6, un groupement aryle substitué ou non substitué, de préférence un phényle substitué ou non substitué, un groupement benzyle ou un phénoxyalkyle dans

lequel le résidu alkyle a 1 à 6 atomes de carbone ; ou
f) un groupement ester d'acides inorganiques,
g) $-SiR_aR_bR_c$ dans lequel R_a, R_b, R_c sont indépendamment choisis parmi un groupement alkyle C_1-C_4 ou aryle, de préférence un groupement phényle,

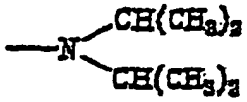
à condition que R' ne soit ni un atome d'hydrogène, ni un groupement méthyle ou benzyle si R est un atome d'hydrogène, R n'est pas un groupement éthyle si R' est un atome d'hydrogène,
X représente un groupement amine tertiaire de formule Ia



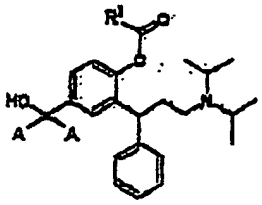
Formule Ia

dans lequel R^8 et R^9 représentent des groupements d'hydrocarbyles non-aromatiques, qui peuvent être identiques ou différents et qui contiennent en même temps au moins trois atomes de carbone, et dans lesquels R^8 et R^9 peuvent former un cycle ainsi que l'azote de l'amine.
Y et Z représentent indépendamment une liaison simple entre le groupement $(CH_2)_n$ et le groupement carbonyle, O, S ou NH,
A représente un atome d'hydrogène (^1H) ou de deutérium (^2H),
n est compris entre 0 et 12
et
leurs sels avec des acides physiologiquement acceptables, leurs bases libres et, quand les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères uniques.

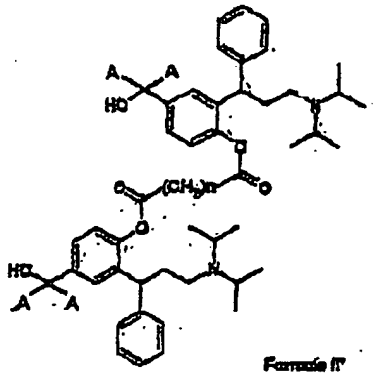
2. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 1, dans lesquelles X est



3. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi les monoesters phénoliques représentés par les formules générales II et II'



Formule II



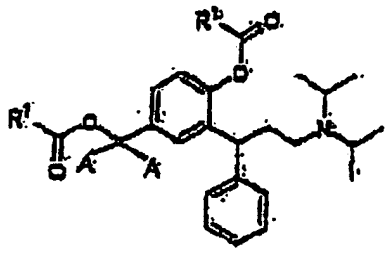
Formule II'

dans lesquelles R^1 représente un atome d'hydrogène, un alkyle C_1-C_6 ou un phényle.

4. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 3 choisies parmi :

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide formique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide propionique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide butyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide isobutyrique,
l'ester de R-(+)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide isobutyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-acétamidoacétique,
l'ester de (+) -2- (3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide cyclopentanecarboxyli-que,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide cyclohexanecarboxyli-que,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide benzoïque,
l'ester de R-(+)-2-(3-diisoproplamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide benzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-hydroxyméthylphényle de l'acide 4-méthylbenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-méthylbenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-acétoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 1-naphtoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-naphtoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 4-chlorobenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 4-méthoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-méthoxybenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-hydroxyméthylphényle de l'acide 4-nitrobenzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide 2-nitrobenzoïque,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide malonique,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide succinique,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide pentanoïque,
l'ester de (±)-bis-[2-(3-diisopropylamino-1-phényl-propyl)-4-hydroxyméthylphényle de l'acide hexadioïque.

5. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi les diesters identiques à ceux représentés par la formule générale III



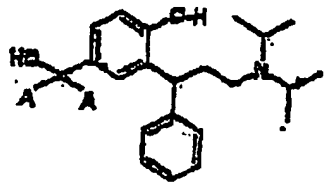
Formule III

dans laquelle R^1 est défini selon la revendication 3

6. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 5 choisies parmi :

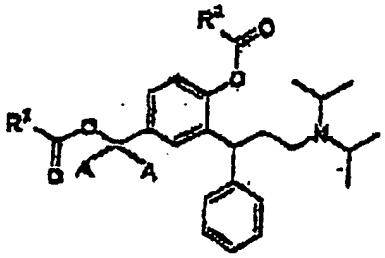
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide formique,

l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-propionyloxyméthylphényle de l'acide propionique,
l'ester de (±)4-n-butyryloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-phényle de l'acide n-butyrique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-isobutyryloxyméthylphényle de l'acide isobutyrique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-benzyle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-benzoyloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-phényle de l'acide benzoïque,
l'ester de R-(+)-4-benzoyloxyméthyl-2-(3-diisopropyl-amino-1-phénylpropyl)-4-(2,2-diméthylpropionyloxy)-phényle de l'acide benzoïque,
les poly-co-DL-lactides de l'intermédiaire B, ledit intermédiaire B ayant la formule



dans laquelle A est défini selon la revendication 1

7. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des diesters mixtes représentées par la formule générale IV



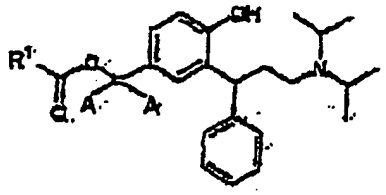
Formula IV

dans laquelle R^1 est défini selon la revendication 3
et
R^2 représente un atome d'hydrogène, un groupement alkyle C^1-C^6 ou un phényle
à condition que R^1 et R^2 ne soient pas identiques

8. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 7 choisies parmi

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-formyloxyméthylphényle de l'acide benzoïque,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-acétoxyméthylphényle de l'acide benzoïque,
l'ester de R-(+)-2-(3-diisopropylamino-1-phénylpropyl)-4-acétoxyméthylphényle de l'acide benzoïque,
l'ester de (±)-4-acétoxyméthyl-2-(3-diisopropylamino-1-phényl-propyl)-phényle de l'acide isobutyrique,
l'ester de R-(+)-4-acétoxyméthyl-2-(3-diisopropylamino-1-phényl-propyl)-phényle de l'acide isobutyrique,
l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phényl propyl)-benzyle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-acétoxy-3-(3-diisopropylamino-1-phényl propyl)-phényle de l'acide 2,2-diméthylpropionique,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide benzoïque.

9. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des monoesters benzyliques représentés par la formule générale V



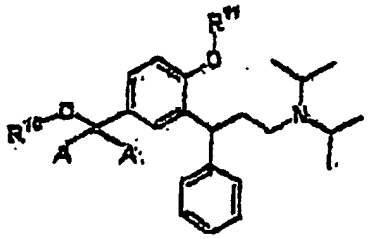
Formule V

dans laquelle R^1 est défini selon la revendication 3

10. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 9 choisies parmi

l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide formique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide acétique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide propionique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide butyrique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide isobutyrique
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide 2,2-diméthylpropionique
l'ester de (±)-3- (3-diisopropylamino-1-phénylpropyl)-4-hydroxybenzyle de l'acide benzoïque

11. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des éthers et des éthers silylés représentées par la formule générale VI



Formule VI

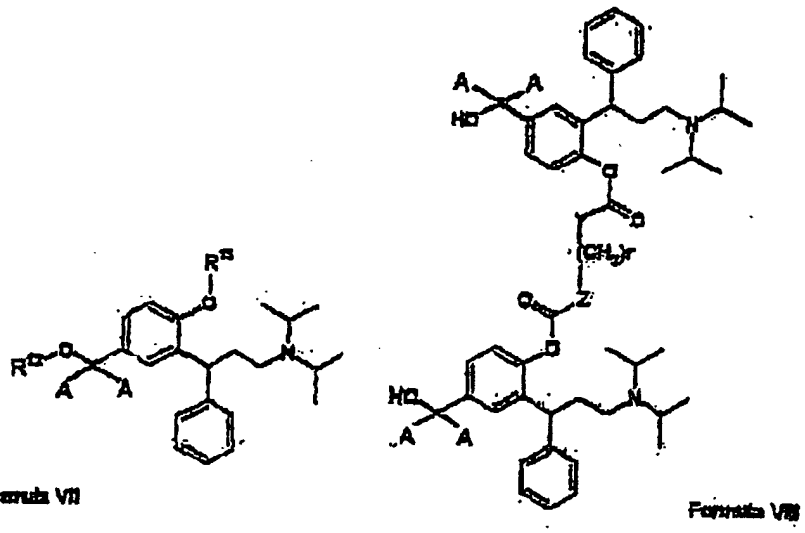
dans laquelle au moins un des substituants R^{10} ou R^{11} est choisi parmi un groupement alkyle C_1-C_6, un benzyle ou $-SiR_aR_bR_c$ selon la revendication 1 et l'autre substituant R^{10} ou R^{11} peut en plus représenter un atome d'hydrogène, un groupement alkyl carbonyle C_1-C_6 ou un benzoyle.

12. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 11 choisies parmi

le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-méthoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-propoxy-méthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-isoprop-oxyméthyl phénol,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-butoxy-méthyl phénol,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-méthoxyméthylphényle de l'acide acétique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxyméthylphényle de l'acide acétique,
le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-tri-méthylsilanyloxyméthyl phénol,
la (±)-diisopropyl-[3-phényl-3-(2-triméthylsilanyloxy-5-tri-méthylsilanyloxyméthyl)-propyl]-amine,
le (±)-[3-(3-diisopropylamino-1-phénylpropyl)-4-tri-méthylsilanyloxyphényl]-méthanol,
la (±)-diisopropyl-[3-(5-méthoxyméthyl-2-triméthyl-silanyloxyphényl)]-3-phénylpropyl-amine,
la (±)-diisopropyl-[3-(5-éthoxyméthyl-2-triméthyl sil-anyloxyphényl)]-3-phénylpropyl-amine,
le (±)-[4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phényl]-méthanol,
l'ester de (±)-4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,

le (±)-4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phénol,
l'ester de (±)-4-(sert.-butyl-diméthylsilanyloxy)-2-(3-diisopropylamino-1-phénylpropyl)-phényle de l'acide acétique,
la (±)-{3-[2-(tert.-butyl-diméthylsilanyloxy)-5-(tert.-butyl-diméthylsilanyloxyl)-phényl]-3-phényl propyl} di-isopropylamine,
le (±)-[4-(tert.-butyl-diméthylsilanyloxy)-3-(3-diiso-propylamino-1-phénylpropyl)-phényl]-méthanol,
l'ester de (±)-4-(tert.-butyl-diphéthylsilanyloxyméthyl)-2-(3-diisopropylamino-1-phénylpropyl)-phényle de l'acide acétique,
le (±)-4-(tert.-butyl-diphéthylsilanyloxyméthyl)-2-(3-diiso propylamino-1-phénylpropyl)-phénol,
la (±)-{3-[2-(tert.-butyl-diméthylsilanyloxy)-5-(tert. -butyl-diphéthylsilanyloxyméthyl)-phényl]-2-phényl-propyl} diisopropylamine,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide acétique,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phénylpropyl)-benzyle de l'acide benzoïque,
l'ester de (±)-4-benzyloxy-3-(3-diisopropylamino-1-phényl-propyl)-benzyle de l'acide isobutyrique,
le (±)-2-(3-diisopropylamino-1-phényl-propyl)-4-(1β-D-glucuronosyloxyméthyl)-phénol.

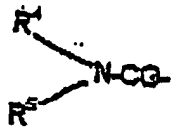
13. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 2 choisies parmi des carbonates et des carbamates représentés par les formules générales VII et VIII



Formule VII

Formule VIII

dans lesquelles Y, Z et n sont définis selon la revendication 1 et dans lesquelles R^{12} et R^{13} représentent un groupement alcoxycarbonyle C_1-C_6 ou



dans lesquelles R^4 et R^5 sont définis selon la revendication 1

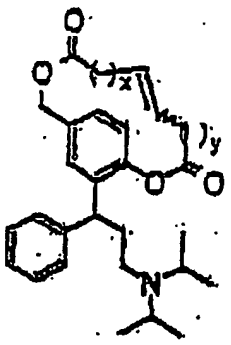
14. 3,3-Diphénylpropylamines comme revendiquées dans la revendication 13 choisies parmi :

l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N-éthylcarbamique,

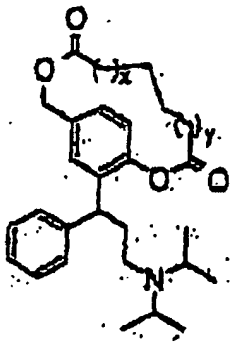
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N,N-diméthylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N,N-diéthylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide N-phénylcarbamique,
l'ester de (±)-[2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphénoxycarbonylamino] éthyle du chlorhydrate de l'acide acétique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N-éthylcarbamoyloxybenzyle de l'acide N,éthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl)-4-N,N-di-méthylcarbamoyloxybenzyle de l'acide N,N-diméthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N, N-diéthylcarbamoyloxybenzyle de l'acide N,N-diéthylcarbamique,
l'ester de (±)-3-(3-diisopropylamino-1-phénylpropyl) -4-N-phénylcarbamoyloxybenzyle de l'acide N-phénylcarbamique,
l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle de l'acide {4-[2-(3-diisopropyl amino-1-phénylpropyl)-4-hydroxyméthyl phénoxycarbonyl-amino]-butyl} carbamique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxyméthylphényle et d'éthyle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-hydroxy-méthylphényle et de phényle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4-éthoxy-carbonyloxyméthylphényle et d'éthyle de l'acide carbonique,
le diester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxy-carbonyloxyméthylphényle et de phényle de l'acide carbonique,

15. 3,3-Diphénylpropylamines choisies parmi :

(i) les composés de formules IX et IX'

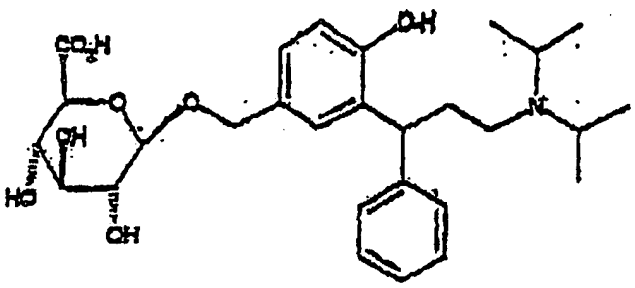


Formule IX



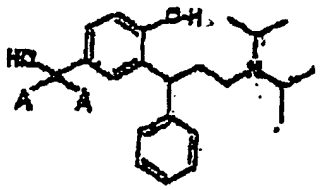
Formule IX'

dans lesquelles x et y sont identiques ou différents et représentent le nombre d'unités méthylènes -(CH_2)- et peuvent être compris entre 0 et 6,
(ii) l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-éthoxysulphooxyméthylphényle de l'acide benzoïque,
(iii) les poly-co-DL-lactides-2-(3-diisopropyl amino-1-phénylpropyl)-4-hydroxyméthyl-phénol,
(iv) le (±)-2-(3-diisopropylamino-1-phénylpropyl)-4-(1β-D-glucuronosyloxyméthyl)-phénol ayant la formule



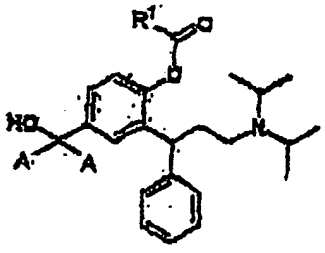
(v) l'ester de (±)-2-(3-diisopropylamino-1-phénylpropyl) -4- (pent-4-enoyloxyméthyl) -phényle de l'acide pent-4-énoïque,
(vi) le 1,8-dioate d'oct-4-ène cyclique de l'intermédiaire B,
(vii) le 1,8-dioate d'octane cyclique de l'intermédiaire B

ledit intermédiaire B ayant la formule



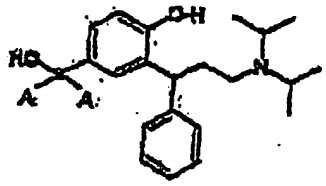
dans laquelle A est selon la revendication 1
et
leurs sels avec des acides physiologiquement acceptables, leurs bases libres et, quand les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères uniques.

16. Procédé pour la production de monoesters phénoliques représentés par la formule générale II



Formule II

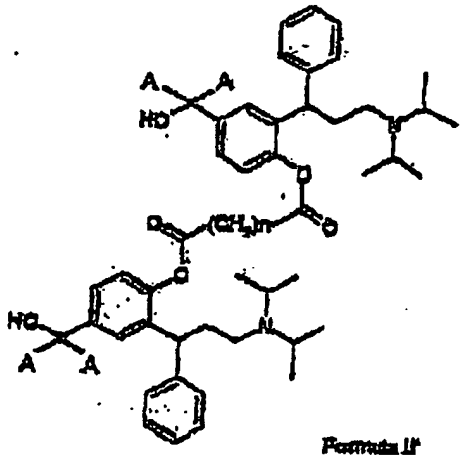
selon la revendication 3, qui comprend le traitement d'un composé de formule



avec un équivalent d'un agent acyclique choisi parmi

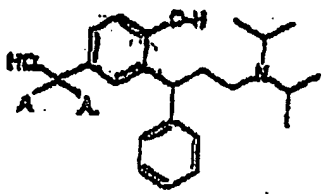
dans lequel LG représente un groupe partant choisi parmi les halogénures, les carboxylates et les imidazoles et R^1 est selon la revendication 3, dans un solvant inerte en présence d'un agent de condensation.

17. Procédé pour la production de monoesters phénoliques représentés par la formule générale II'

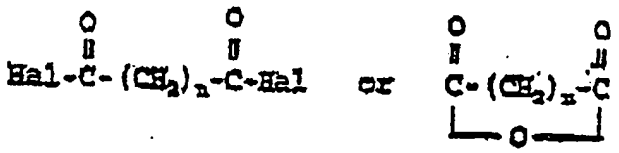


Formule II'

selon la revendication 3, qui comprend le traitement de deux équivalents d'un composés de formule

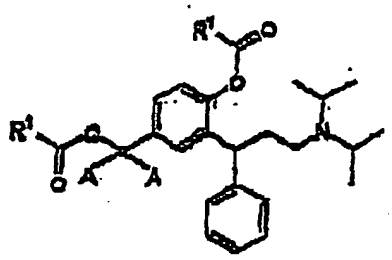


avec un agent d'acylation choisi parmi



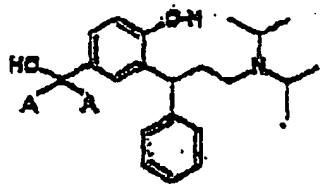
dans lequel Hal représente un atome d'halogène

18. Procédé pour la production de diesters identiques représentés par la formule générale III



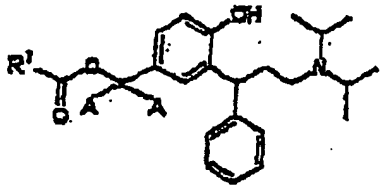
Formule III

selon la revendication 5, qui comprend le traitement d'un composé de formule



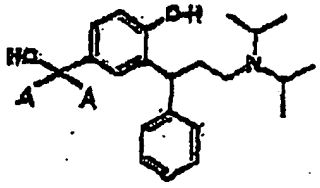
avec au moins deux équivalents d'un agent d'acylation selon la revendication 16.

19. Procédé pour la préparation de monoesters benzyliques représentés par la formule générale V



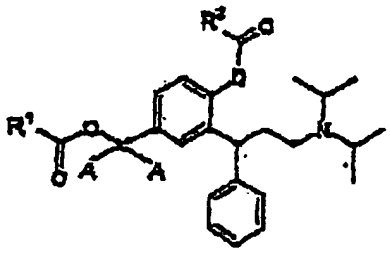
Formule V

selon la revendication 9, qui comprend le traitement d'un composé de formule



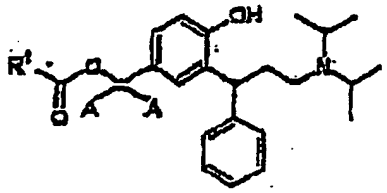
à température ambiante et dans des conditions anhydres avec des esters activés en présence d'enzymes choisies parmi les lipases et les ostérases.

20. Procédé pour la préparation de diesters mixtes représentés par la formule générale IV



Formula IV

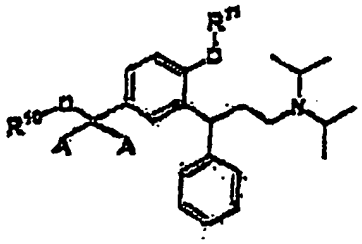
selon la revendication 7, qui comprend l'acylation d'un monoester benzylique représenté par la formule générale V



Formula V

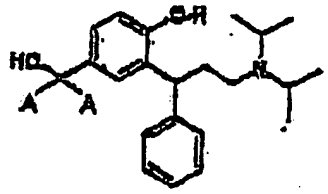
selon la revendication 9 ou par un monoester phénolique représenté par la formule II selon la revendication 3

21. Procédé de production d'éthers représentés par la formule générale VI



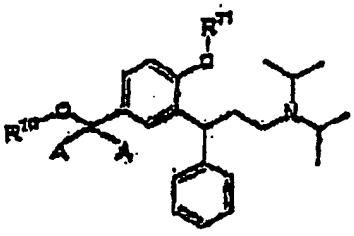
Formula VI

selon la revendication 11 dans laquelle R^{11} est un atome d'hydrogène qui comprend la réaction d'un composé de formule



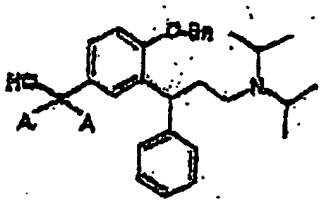
avec un alcool R^{10}-OH en présence d'un catalyseur d'estérification.

22. Procédé pour la préparation d'éthers représentés par la formule générale VI



Formule VI

dans laquelle R^{10} et R^{11} sont selon la revendication 11, qui comprend un traitement acide ou basique d'alcools benzyliques libres choisis parmi



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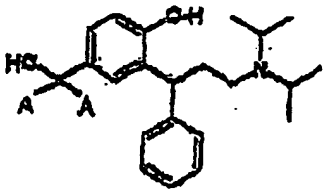

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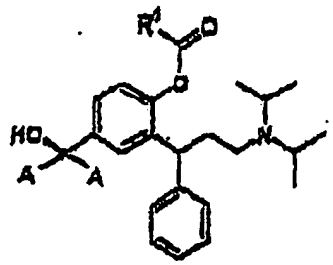
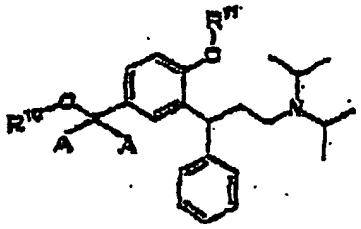


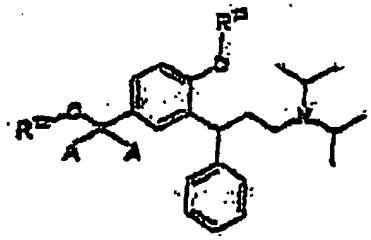
Formule II

ou



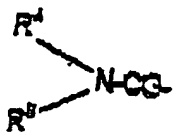
Formule VI

dans lesquelles R^{10} est un atome d'hydrogène et R^{11} est selon la revendication 11 ou

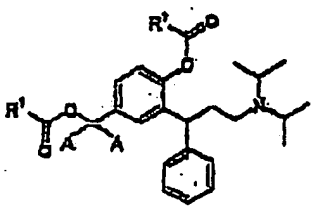


Formule VII

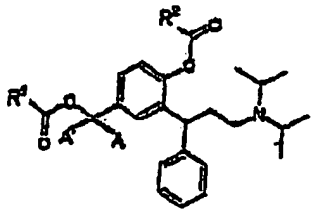
dans laquelle R^{12} est un atome d'hydrogène et R^{13} représente un groupement alcoxycarbonyle ou



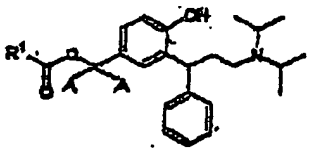
dans lequel R^4 et R^5 sont selon la revendication 1 ou des acylates benzyliques choisis parmi



Formule III



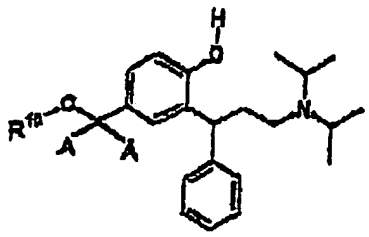
Formule IV



Formule V

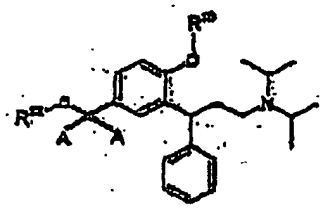
dans lesquels R^1 et R^2 sont selon la revendication 7 en présence de réactifs hydroxylés adéquats

23. Procédé pour la préparation d'éthers de formule VI selon la revendication 11, qui comprend le traitement d'un composé de formule

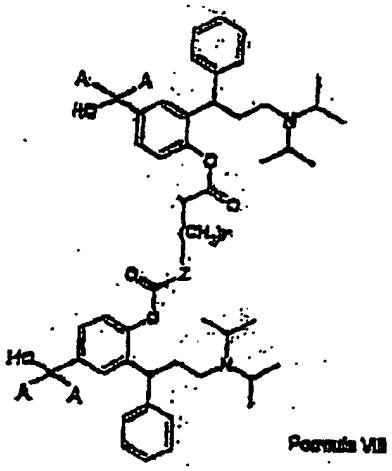


avec un agent d'alkylation choisi parmi les halogénures d'alkyle, les sulfates d'alkyle et les triflates d'alkyle, ledit groupe alkyle ayant 1 à 6 atomes de carbone.

24. Procédé pour la préparation de carbonates et de carbamates représentés par les formules générales VII et VIII

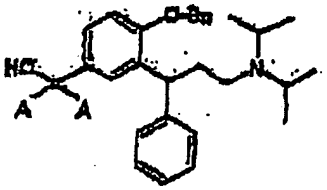


Formule VII

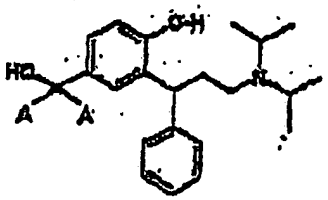


Formule VIII

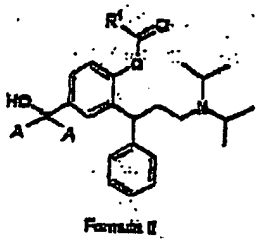
selon la revendication 13, qui comprend la réaction d'un composé choisi parmi le groupe constitué de



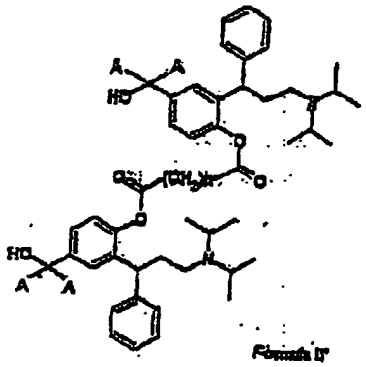
Intermédiaire A



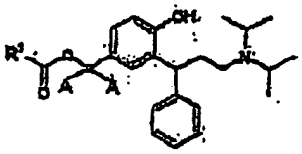
Intermédiaire B



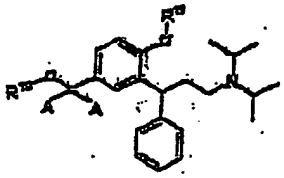
Formule II



Formule IV



Formule V



Formule VI

dans lequel R^1 est selon la revendication 3, n est compris entre 0 et 12, Bn est un groupement benzyle, l'un des substituants R^{10} et R^{11} est un atome d'hydrogène et l'autre est selon la revendication 11 avec des composés carbonylés activés ou des réactifs précurseurs de carbonyles choisis parmi les halogénoformates , les cétènes, les esters activés, les anhydrides mixtes d'acides organiques ou inorganiques, les isocyanates et les isothiocyanates.

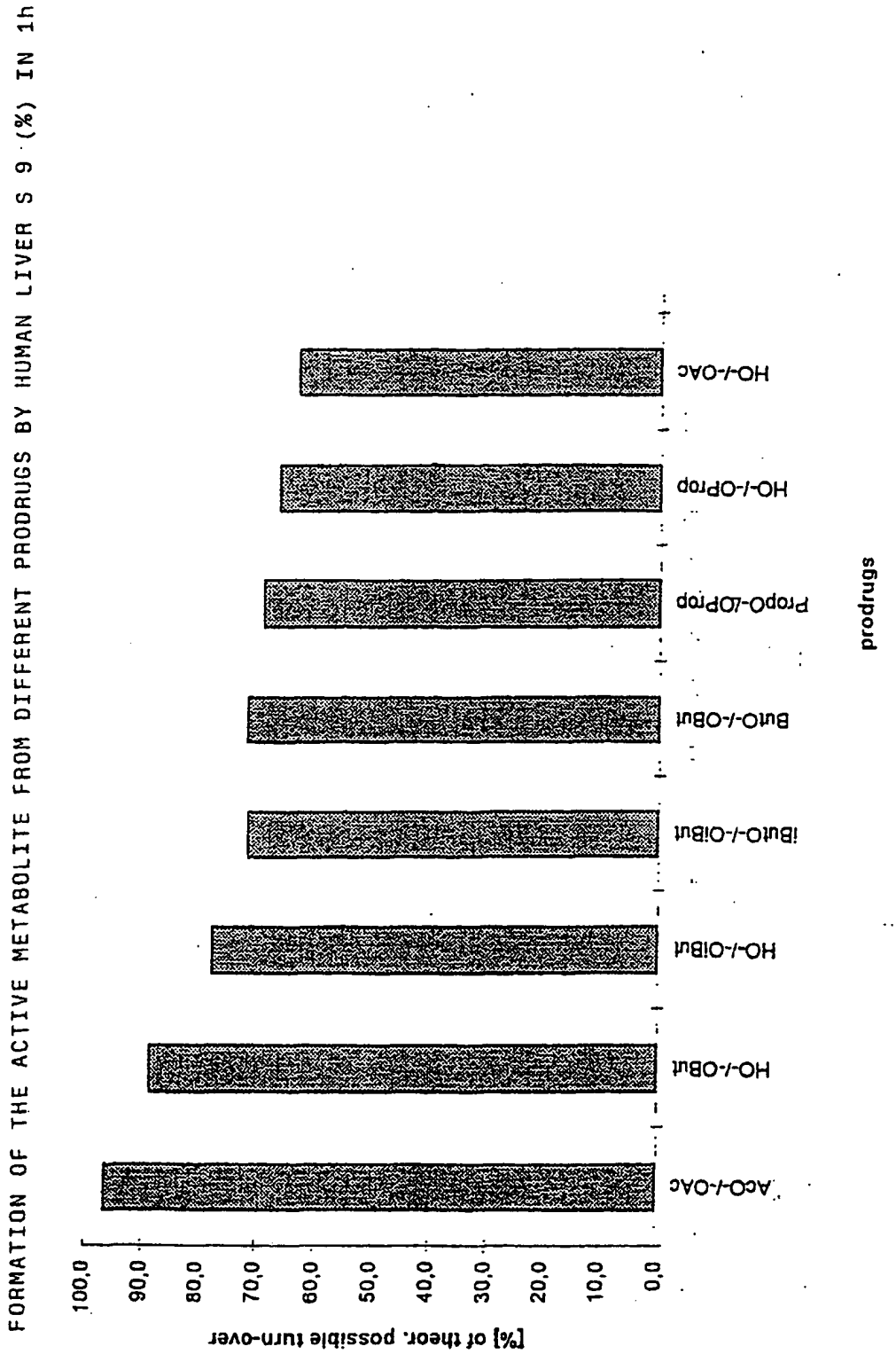
25. 3,3-Diphénylpropylamines comme revendiquées dans les revendications 1 à 15 choisies pour un usage en tant que substances actives pharmaceutiques, surtout en tant qu'agents antimuscariniques.

26. Compositions pharmaceutiques comprenant une 3,3-diphénylpropylamine comme revendiquée dans les revendications 1 à 15 et un support pharmaceutique compatible

27. Composition pharmaceutique comme revendiquée dans la revendication 26 qui est une formulation en pastille.

28. Utilisation d'une 3,3-diphénylpropylamine comme revendiquée dans les revendications 1 à 15 pour préparer un médicament antimuscarinique.

FIG. 1



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PCT/SE99/02052

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(54) **NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT**

NEUE KÜGELCHEN MIT KONTROLLIERTER FREISETZUNG, EIN VERFAHREN ZU DEREN HERSTELLUNG UND DIESE ENTHALTENDE FORMULIERUNG DES TYPS "MULTIPLE UNIT"

NOUVELLES PERLES A LIBERATION CONTROLEE, METHODE DE PRODUCTION, ET FORMULATION MULTICOUCHE COMPRENANT LEDIT COMPRIME

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(56) References cited:
EP-A2- 0 061 217
WO-A1-96/01621
WO-A1-96/29992

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EP 1 128 819 B1

Description

[0001] The present invention relates to pharmaceutical controlled release beads comprising a drug, to a formulation containing said controlled release beads, and to a method of preparing said beads.

[0002] A common type of controlled release beads comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer.

[0003] An example of such controlled release beads is described in US-A-5,783,215 where each bead comprises (i) a core unit of a soluble or insoluble inert material, (ii) a first layer on the core unit comprising an active ingredient dispersed in a hydrophilic polymer, (iii) an optional second layer of hydrophilic polymer covering the first layer, and (iv) an outermost membrane layer effective for controlled release of the active ingredient.

[0004] In the above and similar controlled release beads it is not uncommon to apply a "sealcoat" in the form of a small amount (e.g. 1-3%) of a water-soluble polymer, such as hydroxypropylmethyl cellulose (HPMC) or polyvinylpyrrolidone (PVP), between the inert core and the layer containing the active ingredient. The purpose thereof is generally to isolate the drug from the core surface in the event that a drug-core chemical interaction is possible, and/or to smooth the surface of the inert core such that the surface area is more consistent from lot to lot to thereby improve the coating quality when the drug layer and the controlled release membrane layers are applied.

[0005] WO96/01621 refers to controlled release beads, optionally layered with a first inner layer of hydrophilic polymer, further layered with an active substance being optionally layered with an outer membrane for controlled release.

[0006] WO96/29992 discloses a controlled release diltiazem formulation comprising inert cores layered with the active substance and further layered with a polymeric coating material.

[0007] EP 0061 217 A2 describes an Ibuprofen containing sustained release pharmaceutical composition comprising spheroids consisting of a core and a layer of active principle applied on the core and an outer coating of active excipient forming the sustained release membrane.

[0008] According to the present invention, it has now surprisingly been found that by applying a relatively thick layer of a water-insoluble polymer to the inert core as a sealcoat, several advantages may be obtained in addition to those mentioned above.

[0009] Firstly, in case of a soluble core like one of sugar, for example, the amount of time that the solution within the bead would be saturated with respect to drug may be maximized. Thus, by preventing the soluble core from being a reservoir for drug dissolution, the relative time that a saturated solution would remain within the bead during the release period can be increased considerably. This means that a substantially longer zero order drug release phase (the phase when the drug release rate is essentially constant) will be obtained (and less in the undesirable declining release rate phase). In other words, generally, the use of a thick sealcoat layer will permit the drug release profile to be altered in a predictable fashion, in particular for drugs with a moderate to high water solubility. Also, without drug migrating into the sealcoat, all drug will get released.

[0010] Secondly, the potential influence of the core material on drug release, in particular osmotic pressure or swelling of the core material which could potentially cause internal pressure and film rupture, may be minimized.

[0011] Thirdly, the substantial initial lag phase (no or very low amount of drug release early) that is generally observed with the prior art controlled release beads, especially for slower release formulations where the water influx is slower, may be substantially reduced or eliminated relatively independently of the steady state release rate.

[0012] Therefore, in a first aspect, the present invention provides a controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material having;
(ii) a first layer on the core unit of a substantially water-insoluble polymer;
(iii) a second layer covering the first layer and containing an active ingredient; and
(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

[0013] The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

[0014] The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

[0015] Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

[0016] Usually, the first layer (ii) above constitutes more than 2% (w/w) of the final bead composition, preferably more than 3% (w/w), e.g. from 3% to 80% (w/w).

[0017] The amount of the second layer (ii) above usually constitutes from 0.05 to 60 % (w/w), preferably from 0.1 to 30 % (w/w) of the final bead composition.

[0018] The amount of the third layer (iv) above usually constitutes from 1 to 50 % (w/w), preferably from 2 to 25 % (w/w) of the final bead composition.

[0019] The core unit typically has a size in the range of from 0.05 to 2 mm.

[0020] In a second aspect, the present invention provides a multiple unit formulation comprising said controlled release beads, such as a capsule or a tablet.

[0021] The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. Especially, the beads are spheres of sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

[0022] The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (latex or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

[0023] The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

[0024] A wide variety of therapeutically active agents may be used in conjuction with the present invention. While the therapeutic agent usually is a low or medium dose drug, also high-dose drugs may be contemplated for use in the present invention. The therapeutic agent is preferably a soluble or moderately water-soluble drug (e.g. having a solubility corresponding to from less than 1 to about 30 ml of water per gram of solute at a temperature between 15 °C and 25 °C).

[0025] The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

[0026] Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

[0027] In a third aspect, the present invention provides a method for producing the controlled release beads and formulation, respectively. This method comprises the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;
b) applying a first layer of a substantially water-insoluble polymer to said core;
c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and
d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

[0028] Optionally, the method comprises the further step of applying one or more additional polymer layers to the core as has been mentioned above.

[0029] The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or

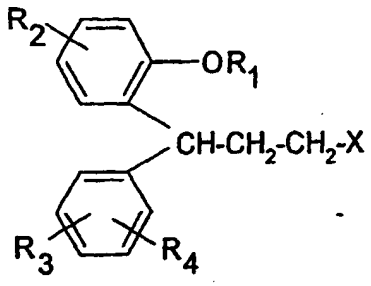
compressing the beads into tablets.

[0030] The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

[0031] After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

[0032] The pharmaceutical formulation of the invention may be administered orally.

[0033] An exemplary class of compounds which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. An exemplary specific compound is tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

[0034] Useful analogues to the above compounds are disclosed in WO 98/43942.

[0035] The above as well as the latter compounds have anti-cholinergic activity and may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The compounds also have spasmolytic activity and may be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

[0036] Specifically, the beads and multiple unit formulation, respectively, according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

[0037] Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urge incontinence, urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine. A salient feature of tolterodine is that it has considerably less side-effects than the previously conventionally used drug, oxybutynin, especially regarding the propensity to cause

dry mouth.

[0038] When tolterodine is the active ingredient in the controlled release bead, the fraction of active ingredient that is released in vitro is preferably not more than 30% after 1 hour, from 40 to 85% after 3 hours, and not less than 80% after 7 hours.

[0039] Administration of the controlled release formulation according to the present invention permits a well controlled release of tolterodine, and thereby a substantially constant serum level of active moiety or moieties to be maintained in the patient for at least 24 hours.

[0040] By the term "active moiety or moities" is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

[0041] The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, $AUC\tau$ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

[0042] For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

[0043] Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

[0044] Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e. g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

[0045] The invention will now be described in more detail by the following nonlimiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with different sealcoat thicknesses; and

Fig. 2 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with 14 % (w/w) and 0 % (w/w) seal coat, respectively. The polymer composition in the third layer of the beads with 0 % sealcoat has been adjusted in order to produce approximately similar initial drug release as from beads with 14 % sealcoat.

EXAMPLE 1

[0046] An exemplary bead containing tolterodine L-tartrate as active ingredient has the following structure:

Core: Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;

First layer: Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, con-

sisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;

Second layer: Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1;
purpose: drug supply;

Third layer: Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1;
purpose: drug release rate control;

[0047] Beads with a three-layer coating having the above characteristics were prepared as follows:

[0048] 1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

[0049] After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

[0050] Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer: HPMC; comprises about 1 % w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

[0051] In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Study of effect of sealcoat thickness

[0052] The effect of the sealcoat thickness on drug release was tested as follows.

[0053] Four lots of 20-25 mesh beads were prepared that contained (i) a Surelease® sealcoat layer at 0, 2, 10 or 14% level, (ii) an HPMC/drug (tolterodine L-tartrate) layer at 4% level (drug:HPMC ratio =5:4), (iii) a Surelease®/HPMC layer at 10% level (Surelease®:HPMC ratio = 6:1 ratio), and (iv) a final HPMC layer at 1%. These were prepared essentially as described above and cured 1 hr at 70 °C.

[0054] Note that the coating level for layer (i) is expressed relative to the sum of the core plus sealcoat while coating levels for layers (ii-iv) are expressed relative to the final coated bead weight.

[0055] A fifth lot of beads was also manufactured identical to the 0% sealcoat lot described above except that the third coating layer was modified (increase in the Surelease®: HPMC layer from a 6:1 to a 11:1) such that the initial drug release rate was similar to the 14% sealcoat formulation described above.

[0056] The in vitro drug release at 37°C in phosphate buffer pH 6.8 with addition of 0.22M potassium chloride was measured. The USP dissolution test apparatus 1 was used. The results are shown in the diagrams in Fig. 1 and 2. As shown in Fig. 1, as the sealcoat layer gets thicker, the drug release rate both decreases and becomes more zero-order.

[0057] Fig. 2 shows the comparison of the 0% sealcoat formulation (11:1 Surelease®: HPMC) to the 14% sealcoat (6:1 the Surelease®: HPMC). It can be seen that, after a slight lag period observed by the 0% sealcoated beads, the

initial drug release rates are similar. However, after approximately 15-20% of the drug is released, the release rate from beads with 0 % sealcoat beads falls while release rate from the 14% sealcoat remains extremely zero order. Indeed, for the 0 % sealcoat beads the release rate between 45-60% is only approximately half of the initial (first 20 %) release rate. Comparatively, for the 14% sealcoat lot, the release rate between 45-60% range is identical to the rate over the first 20%.

[0058] In an analogous manner to the procedure described in Example 1 above, other exemplary bead formulations containing tolterodine L-tartrate as the active ingredient were prepared as described in Examples 2 and 3 below.

EXAMPLE 2

[0059] 400 g of sugar spheres (20-25 mesh, Edward Mendell Co, USA) were charged into a top-spray fluid bed coater (Nica, Sweden) and coated with Surelease® and thereafter cured in a drying cabinet at 70°C for 5 hours.

[0060] A solution of tolterodine-L-tartrate and hydroxypropyl cellulose (HPC) in water was sprayed onto the coated cores.

[0061] The spheres obtained were then coated with a mixture of ethylcellulose, hydroxypropylcellulose and triethyl-citrate (plasticizer). The coating materials were dissolved in a mixture of dichlormethane and ethanol.

[0062] The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	75.7
Surelease®	13
Tolterodine L-tartrate	4.9
HPC	1.5
Ethylcellulose	4.3
Triethyl citrate	0.6

[0063] The obtained spheres showed extended release of tolterodine L-tartrate over at least 10 hours. The release rate was essentially constant.

EXAMPLE 3

[0064] 4800 g of sugar spheres (18-20 mesh, Mendell, USA) were coated in a Wurster fluid bed with Surelease® to a theoretical weight gain of 10 % and thereafter cured in a drying cabinet at 60°C for 6 hours.

[0065] A solution of tolterodine L-tartrate and hydroxypropylmethyl cellulose (HPMC) in water was sprayed onto 1200 g of the cured sphere cores.

[0066] 1000 g of the obtained spheres were then coated by spraying with an aqueous dispersion of a cross-linked latex of hydroxyl-end blocked polydimethylsiloxan (PDMS, Dow Corning; USA) and colloidal silica (Dow Corning, USA) to a theoretical weight gain of 15%.

[0067] The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	76
Surelease®	7.8
Tolterodine L-tartrate	2.8
HPMC	0.4
PDMS	8.7
Colloidal silica	4.3

[0068] The obtained spheres showed extended release of tolterodine L-tartrate over at least 11 hours. The release rate was nearly constant.

Claims

1. A controlled release bead comprising:

   (i) a core unit of a substantially water-soluble or water-swellable inert material;
   (ii) a first layer on the core unit of a substantially water-insoluble polymer,

(iii) a second layer covering the first layer and containing an active ingredient; and
(iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

2. The bead according to claim 1, wherein the amount of polymer in said first layer is sufficient to substantially retard water penetration into the core.

3. The bead according to claim 1 or 2, wherein the thickness of said first layer is sufficient to affect the drug release rate from the bead.

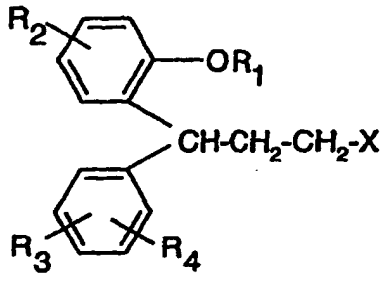
4. The bead according to claim 1, 2 or 3, wherein the amount of the first layer constitutes more than 2% (w/w), preferably more than 3% (w/w) of the final bead composition.

5. The bead according to any one of claims 1 to 4, wherein the amount of said second layer usually constitutes from 0.05 to 60 % (w/w), preferably from 0.1 to 30 % (w/w) of the final bead composition.

6. The bead according to any one of claims 1 to 5, wherein the amount of said third layer usually constitutes from 1 to 50 % (w/w), preferably from 2 to 25 % (w/w) of the final bead composition.

7. The bead according to any one of claims 1 to 6, wherein said third polymer layer is coated with a fourth layer of a water-soluble polymer or an additional functional coating.

8. The bead according to any one of claims 1 to 7, wherein said active ingredient is selected from compounds having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

9. The bead according to claim 8, wherein said active ingredient is selected from tolterodine, the 5-hydroxymethyl metabolite of tolterodine, the (S)-enantiomer of tolterodine, the 5-hydroxymethyl metabolite of the (S)-enantiomer of tolterodine, the racemate of tolterodine, and prodrug forms and pharmacologically acceptable salts thereof.

10. The bead according to claim 9, wherein said active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

11. The bead according to claim 10, wherein the fraction of active ingredient that is released in vitro is not more than

30% after 1 hour, from 40 to 85% after 3 hours, and not less than 80% after 7 hours.

12. The bead according to any one of claims 1 to 11, wherein the polymer material of said first layer comprises ethyl cellulose.

13. The bead according to any one of claims 1 to 12, wherein said second layer comprises hydroxypropylmethyl cellulose as binder.

14. The bead according to any one of claims 1 to 13, wherein the polymer material of said third layer comprises a combination of hydroxypropylmethyl cellulose and ethyl cellulose.

15. The bead according to any one of claims 1 to 14, wherein the core unit has a size of 0.05 to 2 mm.

16. A multiple unit formulation comprising a controlled release bead according to any one of claims 1 to 15.

17. The multiple unit formulation according to claim 16 which is a capsule.

18. A method of producing a controlled release bead, which method comprises the steps of:

a) providing a core unit of a substantially water-soluble or water-swellable material;
b) applying a first layer of a substantially water-insoluble polymer to said core;
c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and
d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first is selected to provide a layer thickness that permits control of water penetration into the core.

19. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating overactive bladder.

20. Use according to claim 19, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

21. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating nocturia.

22. Use according to claim 21, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

23. Use of therapeutically effective amount of beads according to any one of claims 8 to 15 for the preparation of a medicament for treating gastrointestinal disorders.

Patentansprüche

1. Perle mit gesteuerter Freisetzung, umfassend

i. eine Kerneinheit aus einem im wesentlichen wasser-löslichen oder in Wasser quellbaren inerten Material;
ii. eine erste Schicht aus einem im wesentlichen wasser-unlöslichen Polymer auf der Kerneinheit;
iii. eine zweite Schicht, die die erste Schicht bedeckt und einen Wirkstoff enthält, und
iv. eine dritte Schicht aus Polymer auf der zweiten Schicht, die wirksam ist zur gesteuerten Freisetzung des Wirkstoffs,

wobei die erste Schicht geeignet ist, das Eindringen von Wasser in den Kern zu steuern.

2. Perle nach Anspruch 1, wobei die Menge an Polymer in der ersten Schicht ausreichend ist, um das Eindringen von Wasser in den Kern wesentlich zu verzögern.

3. Perle nach Anspruch 1 oder 2, wobei die Dicke der ersten Schicht ausreichend ist, um die Freisetzungsgeschwindigkeit des Arzneimittels aus der Perle zu beeinflussen.

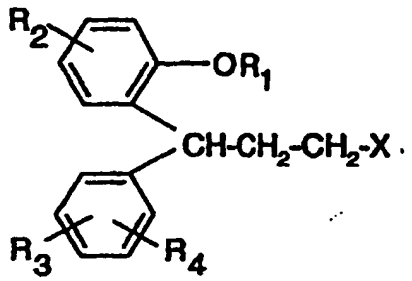
4. Perle nach Anspruch 1, 2 oder 3, wobei die Menge der ersten Schicht mehr als 2 Gew.%, vorzugsweise mehr als 3 Gew.%, der gesamten Perlenzusammensetzung ausmacht.

5. Perle nach einem der Ansprüche 1 bis 4, wobei die Menge der zweiten Schicht üblicherweise 0,05 bis 60 Gew.%, vorzugsweise 0,1 bis 30 Gew.%, der gesamten Perlenzusammensetzung ausmacht.

6. Perle nach einem der Ansprüche 1 bis 5, wobei die Menge der dritten Schicht üblicherweise 1 bis 50 Gew.%, vorzugsweise 2 bis 25 Gew.%, der gesamten Perlen-Zusammensetzung ausmacht.

7. Perle nach einem der Ansprüche 1 bis 6, wobei die dritte Polymerschicht mit einer vierten Schicht aus einem wasser-löslichen Polymer oder einem zusätzlichen funktionellen Überzug überzogen ist.

8. Perle nach einem der Ansprüche 1 bis 7, wobei der Wirkstoff ausgewählt ist aus Verbindungen der allgemeinen Formel



wobei R_1 Wasserstoff oder Methyl bedeutet, R_2, R_3 und R_4 unabhängig Wasserstoff, Methyl, Methoy, Hydroxy, Hydroxymethyl, Carbamoyl, Sulfamoyl oder Halogen bedeuten und X eine tertiäre Aminogruppe $-NR_5R_6$ bedeutet, wobei R_5 und R_6 nichtaromatische Kohlenwasserstoff-Gruppen, die gleich oder verschieden sein können, insbesondere C_1-C_6-Alkyl oder Adamantyl, bedeuten und die zusammen mindestens 3, vorzugsweise mindestens 4 Kohlenstoffatome enthalten, und von denen jede einen Hydroxy-Substituenten enthalten kann, und wobei R_5 und R_6 zusammen mit dem Amin-Stickstoff einen Ring, vorzugsweise einen nicht-aromatischen Ring, der kein Heteroatom außer dem Amin-Stickstoff enthält, bilden können, ihre Salze mit physiologisch annehmbaren Säuren und, wenn die Verbindungen in Form von optischen Isomeren vorliegen können, dem razemischen Gemisch und den einzelnen Enatiomeren.

9. Perle nach Anspruch 8, wobei der Wirkstoff ausgewählt ist aus Tolterodin, dem 5-Hydroxymethyl-Metaboliten von Tolterodin, dem (S)-Enantiomer von Tolterodin, dem 5-Hydroxymethyl-Metaboliten des (S)-Enantiomers von Tolterodin, dem Razemat von Tolterodin, und Vor-Arzneimittelformen und pharmakologisch annehmbaren Salzen davon.

10. Perle nach Anspruch 9, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

11. Perle nach Anspruch 10, wobei der Anteil an Wirkstoff, der in vitro freigesetzt wird, nach 1 Stunde nicht mehr als 30%, nach 3 Stunden 40 bis 85% und nach 7 Stunden nicht weniger als 80% beträgt.

12. Perle nach einem der Ansprüche 1 bis 11, wobei das Polymer-Material der ersten Schicht Ethylcellulose umfaßt.

13. Perle nach einem der Ansprüche 1 bis 12, wobei die zweite Schicht Hydroxypropylmethyl-celulose als Bindemittel umfaßt.

14. Perle nach einem der Ansprüche 1 bis 13, wobei das Polymer-Material der dritten Schicht eine Kombination von Hydroxypropylmethyl-celulose und Ethylcellulose umfaßt.

15. Perle nach einem der Ansprüche 1 bis 14, wobei die Kemeinheit eine Größe von 0,05 bis 2 mm hat.

16. Zubereitung mit mehreren Einheiten, umfassend eine Perle mit gesteuerter Freisetzung nach einem der Ansprüche 1 bis 15.

17. Zubereitung mit mehreren Einheiten nach Anspruch 16, die eine Kapsel ist.

18. Verfahren zur Herstellung einer Perle mit gesteuerter Freisetzung, wobei das Verfahren die folgenden Stufen umfaßt:

a) Bereitstellen einer Kerneinheit aus einem im wesentlichen wasser-löslichen oder in Wasser quellbaren Material;
b) Aufbringen einer ersten Schicht aus einem im wesentlichen wasser-unlöslichen Polymer auf den Kern;
c) Aufbringen einer zweiten Schicht, umfassend einen Wirkstoff und gegebenenfalls ein Polymer-Bindemittel, auf die erste Schicht und
d) Aufbringen einer dritten Polymer-Schicht, die wirksam ist zur gesteuerten Freisetzung des Wirkstoffs, auf die zweite Schicht,

wobei die Menge an Material in der ersten (Schicht) so ausgewählt wird, daß eine Schichtdicke entsteht, die es ermöglicht, das Eindringen von Wasser in den Kern zu steuern.

19. Verwendung einer therapeutisch wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung einer überaktiven Blase.

20. Verwendung nach Anspruch 19, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

21. Verwendung einer wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung von Nocturie.

22. Verwendung nach Anspruch 21, wobei der Wirkstoff Tolterodin oder ein pharmakologisch annehmbares Salz davon ist.

23. Verwendung einer therapeutisch wirksamen Menge an Perlen nach einem der Ansprüche 8 bis 15 zur Herstellung eines Arzneimittels zur Behandlung von gastrointestinalen Störungen.

Revendications

1. Perle à libération contrôlée comprenant :

(i) une unité noyau en un matériau inerte sensiblement hydrosoluble ou expansible dans l'eau ;
(ii) une première couche sur l'unité noyau en un polymère sensiblement insoluble dans l'eau ;
(iii) une deuxième couche couvrant la première couche et contenant un principe actif ; et
(iv) une troisième couche de polymère sur la deuxième couche efficace pour une libération contrôlée du principe actif,

dans laquelle ladite première couche est adaptée pour contrôler la pénétration de l'eau dans le noyau.

2. Perle selon la revendication 1, dans laquelle la quantité de polymère dans ladite première couche est suffisante pour retarder sensiblement la pénétration de l'eau dans le noyau.

3. Perle selon la revendication 1 ou 2, dans laquelle l'épaisseur de ladite première couche est suffisante pour affecter le taux de libération d'une substance médicamenteuse à partir de la perle.

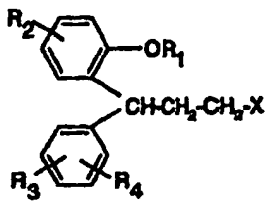
4. Perle selon la revendication 1, 2 ou 3, dans laquelle la quantité de la première couche représente plus de 2% (m/m), de préférence plus de 3% (m/m) de la composition finale de la perle.

5. Perle selon l'une quelconque des revendications 1 à 4, dans laquelle la quantité de ladite deuxième couche représente en règle générale de 0,05 à 60 % (m/m), de préférence de 0,1 à 30 % (m/m) de la composition finale de la perle.

6. Perle selon l'une quelconque des revendications 1 à 5, dans laquelle la quantité de ladite troisième couche représente en règle générale de 1 à 50 % (m/m), de préférence de 2 à 25 % (m/m) de la composition finale de la perle.

7. Perle selon l'une quelconque des revendications 1 à 6, dans laquelle ladite troisième couche de polymère est revêtue d'une quatrième couche d'un polymère hydrosoluble ou d'un revêtement fonctionnel additionnel.

8. Perle selon l'une quelconque des revendications 1 à 7, dans laquelle ledit principe actif est choisi parmi des composés ayant la formule générale suivante :



dans laquelle R_1 représente l'hydrogène ou le méthyle ; R_2, R_3 et R_4 sont de façon indépendante l'hydrogène, méthyle, métoxy, hydroxy, hydroxyméthyle, carbamoyl, sulphamoyl ou halogène; et X représente un groupe amino tertiaire - NR_5,R_6, dans lequel R_5 et R_6 sont des groupes hydrocarbyles non aromatiques, pouvant être identiques ou différents, en particulier un C_{1-6} -alkyle ou adamantyl, et contenant ensemble au moins trois, de préférence au moins quatre atomes de carbone, chacun d'entre eux pouvant porter un substituant hydroxy, et dans lequel R_5 et R_6 peuvent former un cycle conjointement avec l'azote de l'amine, de préférence un cycle non-aromatique n'ayant pas d'autre hétéroatome que l'azote de l'amine, leurs sels avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous la forme d'isomères optiques, le mélange racémique et les énantiomères individuels.

9. Perle selon la revendication 8, dans laquelle ledit principe actif est choisi parmi la toltérodine, le métabolite 5-hydroxyméthyle de la toltérodine, le (S)-énantiomère de la toltérodine, le métabolite 5-hydroxyméthyle du (S)-énantiomère de la toltérodine, le racémique de la toltérodine, ainsi que des formes de pro-médicaments et leurs sels pharmaceutiquement acceptables.

10. Perle selon la revendication 9, dans laquelle ledit principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

11. Perle selon la revendication 10, dans laquelle la fraction du principe actif qui est libérée in vitro ne dépasse pas 30 % après une heure, est de 40 à 85 % après trois heures, et n'est pas en-deçà de 80 % après sept heures.

12. Perle selon l'une quelconque des revendications 1 à 11, dans laquelle le matériau polymère de ladite première couche comprend l'éthylcellulose.

13. Perle selon l'une quelconque des revendications 1 à 12, dans laquelle ladite deuxième couche comprend l'hydroxypropylméthylcellulose en tant que liant.

14. Perle selon l'une quelconque des revendications 1 à 13, dans laquelle le matériau polymère de ladite troisième couche comprend une combinaison d'hydroxypropylméthylcellulose et d'éthylcellulose.

15. Perle selon l'une quelconque des revendications 1 à 14, dans laquelle l'unité noyau a une taille de 0,05 mm à 2 mm.

16. Formulation à unités multiples comprenant une perle à libération contrôlée selon l'une quelconque des revendications 1 à 15.

17. Formulation à unités multiples selon la revendication 16 sous forme d'une capsule.

18. Procédé de préparation d'une perle à libération contrôlée, ledit procédé comprenant les étapes suivantes :

a) fournir une unité noyau en un matériau sensiblement hydrosoluble ou expansible dans l'eau ;
b) appliquer une première couche d'un polymère sensiblement insoluble dans l'eau sur ledit noyau ;
c) appliquer sur ladite première couche une deuxième couche comprenant un principe actif et éventuellement un liant polymère ; et
d) appliquer sur ladite deuxième couche une troisième couche polymère efficace pour une libération contrôlée du principe actif ;

dans lequel la quantité de matériau dans ladite première couche est choisie de façon à fournir une épaisseur de couche permettant de contrôler la pénétration de l'eau dans le noyau.

19. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement de l'hyperactivité de la vessie.

20. Utilisation selon la revendication 19, dans lequel le principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

21. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement de la nocturie.

22. Utilisation selon la revendication 21, dans laquelle le principe actif est la toltérodine ou un sel pharmaceutiquement acceptable de celle-ci.

23. Utilisation d'une quantité thérapeutiquement efficace de perles selon l'une quelconque des revendications 8 à 15 pour la préparation d'un médicament destiné au traitement des troubles gastro-intestinaux.

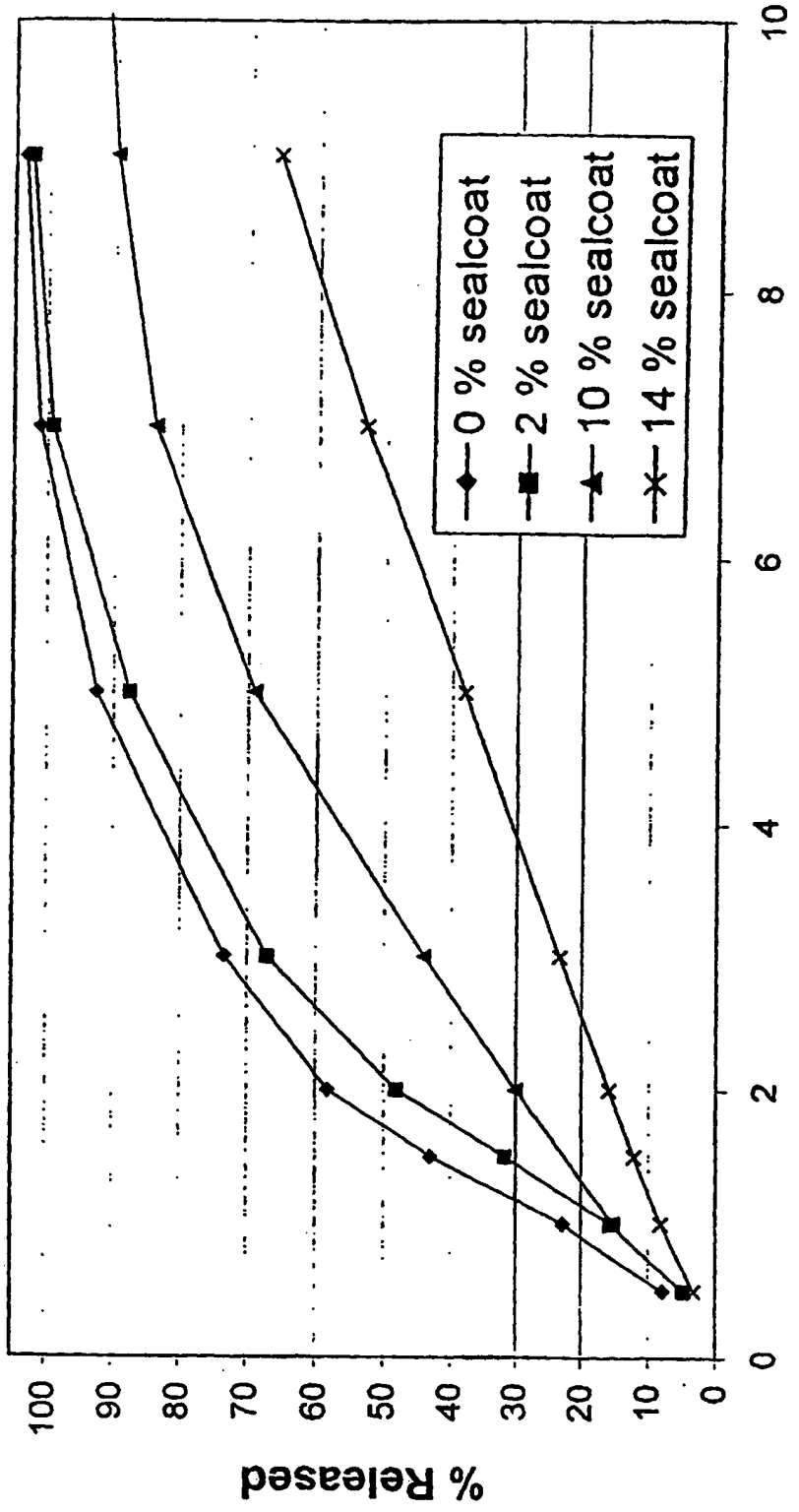


FIG. 1

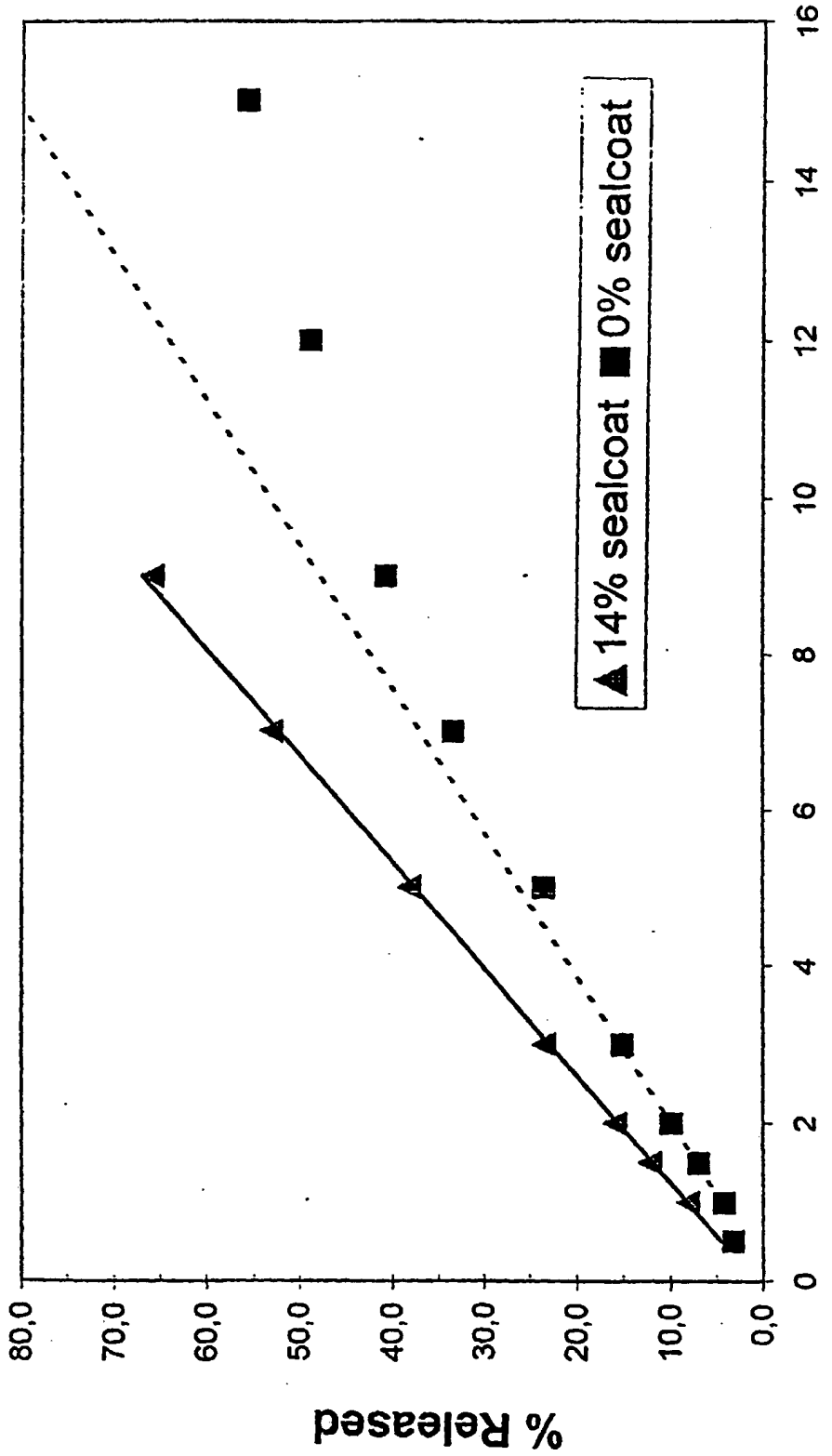


FIG. 2

PATENT SPECIFICATION

624,117

Application Date: Dec. 7, 1946. No. 36257/46.

Complete Specification Left: Dec. 4, 1947.

Complete Specification Accepted: May 27, 1949.

Index at acceptance:—Class 2(iii), B4(a2: d), C2(a2: a14: b3), C3a13a3.

PROVISIONAL SPECIFICATION

Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

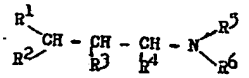
We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company), and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted propylamines which have valuable therapeutic properties.

The object of our invention is to make possible the manufacture of certain novel substituted allylamines which are useful as starting materials for other production compounds.

A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

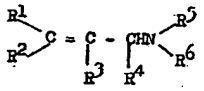
According to the process of our invention we make N-disubstituted-$\gamma\gamma$-disubstituted allylamines of the formula



by the removal of the elements of water from the corresponding N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxy propylamines of the formula

In each of the general formulæ just given R^1 and R^2 are either identical or different and may be aryl, aralkyl or hydroaromatic groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino- or morpholino- groups.

According to a further feature of our invention, we convert the new substituted allylamines, described above, into N-disubstituted-$\gamma\gamma$-disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent (e.g. petroleum ether).

Alternatively in some examples the base may be converted into a salt, particularly the hydrochloride, by treating the dried solution of the base in a solvent (for

example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

The manufacture of the N-disubstituted γγ-disubstituted-γ-hydroxy proplyamines used as starting materials is described in the specification of our co-pending application for Letters Patent No. 36258/46 (Serial No. 624,118) of even date herewith. Examples of such starting materials are γγ-diphenyl-γ-hydroxy-α-piperidinopropane and γγ-diphenyl-γ-hydroxy-α-dimethylaminopropane.

The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.

The manufacture by a different process of some of the N - substituted - γγ - disubstituted propylamines which may be made by the process of our invention has already been described, for example γγ-diphenyl - α - diethylamino - propane (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and γγ-diphenyl-α-piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma.

The invention is illustrated by the following example, in which quantities are given in parts by weight.

A solution of 15 parts γγ - diphenyl-γ-hydroxy - α - piperidinopropane hydrochloride in 30 parts concentrated aqueous hydrochloric acid and 100 parts glacial acetic acid was refluxed for 30 minutes. The solution kas then evaporated to dryness under reduced pressure and the residual solid dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ether solution was dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, γγ - diphenyl-α-piperidino-βγ-propylene, was collected as a colourless liquid, boiling point 138°C. at 0.1 mm. pressure.

Dry hydrogen chloride was passed through a solution of 10 parts of the base in 20 parts chloroform until acid to congo red and dry ether was added until crystallisation commenced. After standing for several hours the precipitate of γγ-diphenyl - α - piperidino - γ - propylene hydrochloride was filtered off and recrystallised from a mixture of chloroform and acetone. It had melting point 209—210°C.

A solution of 5 parts of the hydrochloride in 50 parts ethyl alcohol was shaken at room temperature (17°C.) with 0.1 parts of platinum oxide (prepared according to the directions given in Organic Syntheses, 1932, Collective, Volume 1, page 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen had been absorbed (after aproximately 3 hours) the catalyst was removed by filtration and the alcohol evaporated under reduced pressure. The solid residue was recrystallised from a mixture of alcohol and acetone when γγ - diphenyl - α - piperidinopropane hydrochloride was obtained as crystals, melting point 215—217°C.

Dated this 7th day of December, 1946.
G. H. FRAZER,
Chartered Patent Agent.

COMPLETE SPECIFICATION

Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company), and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

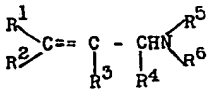
This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted propylamines which have valuable therapeutic properties.

The object of our invention is to make possible the manufacture of certain novel substituted allylamines which have valuable therapeutic activity and are also useful as starting materials for the production of other therapeutically valuable compounds.

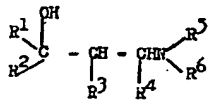
A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic

properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

According to the process of our invention we make N - disubstituted - γγ - disubstituted allylamines of the formula

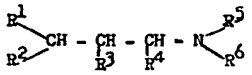


or salts thereof by the removal of the elements of water (by known methods for the conversion of tertiary alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted-γγ-disubstituted - γ - hydroxypropylamines of the formula



or salts thereof. In each of the general formulae just given R^1 and R^2 are aryl, aralkyl or cycloalkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^1 and R^2 may be identical, provided that both are not aralkyl groups; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino-, pyrrolidino- or morpholino- groups.

According to a further feature of our invention, we convert the new substituted allylamines, described above, or their salts, into N - disubstituted - γγ - disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

As a matter of scientific accuracy it may be mentioned that when R^1 or R^2 is an aralkyl or cycloalkyl group or when both R^1 and R^2 are cycloalkyl groups, the allylamine formed by the dehydration step is sometimes an isomer of the allylamine whose general formula is given above, the isomer differing from that of the said general formula only in the position of the double bond and the hydrogen atom. Or the product may be a mixture of such isomers. Both these isomers and mixtures thereof are to be regarded as lying within the scope of our invention, the general formula for these allylamines being read with the position of the double bond and hydrogen atom optional. Both the isomers, of course, yield identical N-disubstituted - γγ - disubstituted propylamines on reduction.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent wherein it is soluble (for example, petroleum ether).

Alternatively in some examples the base may be converted into its hydrochloride, by treating the dried solution of the base in a non-aqueous solvent (for example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

The manufacture of the N - disubstituted - γγ - disubstituted - γ - hydroxy propylamines used as starting materials is described in the Specification of our copending Application for Letters Patent, No. 36258/46 (Serial No. 624,118) of even date herewith. Examples of such starting materials are γγ - diphenyl - γ - hydroxy - α - piperidinopropane and γγ-diphenyl - γ - hydroxy - α - dimethylaminopropane.

The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.

The manufacture by a different process of some of the N substituted - γγ - disubstituted propylamines which may be made by the process of our invention has already been described, for example γγ - diphenyl-

α-diethylaminopropane (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and γγ-diphenyl-α-piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma. By research and experiment we have confirmed the correctness of this claim and have also demonstrated that the allylamines prepared in accordance with this invention likewise have valuable anti-spasmodic, anaesthetic and broncho-dilating activity.

The invention is illustrated by the following examples:—

EXAMPLE 1.

3 - N - Piperidino - 1:1 - diphenylpropan - 1 - ol hydrochloride (15 grams) is dissolved in a mixture of concentrated aqueous hydrochloric acid (30 cubic centimetres) and glacial acetic acid (100 c.c.s) and the solution boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure, the residual solid dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ether solution is dried over anhydrous sodium sulphate, the ether evaporated, and the residual oil distilled under reduced pressure, 3 - N-piperidino - 1:1 - diphenylprop - 1 - ene being collected as a colourles liquid, boiling point 138°C. at 0.1 millimetres pressure.

Dry hydrogen chloride is passed through a solution of the base (10 g.) in chloroform (20 c.c.s) until acid to congo red, and anhydrous ether is added until crystallisation commences. After standing for several hours, the precipitate of 3 - N - piperidino - 1:1 - diphenylprop-1 - ene hydrochloride is filtered off. After recrystallisation from a mixture of chloroform and acetone, the salt has melting point 209—210°C.

The hydrochloride (5 g.) is ethanol (50 c.c.s) is shaken at room temperature with platinum oxide (0.1 g., prepared according to the directions given in Organic Syntheses, 1932, Collective Volume 1, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the ethanol evaporated under reduced pressure. The crystalline residue is recrystallised from a mixture of ethanol and acetone, when 3 - N - piperidino - 1:1 - diphenylpropane hydrochloride is obtained, melting point 215—217°C. The base, liberated from the hydrochloride by treatment with aqueous alkali, has melting point 40—41°C.

EXAMPLE 2.

3 - Dimethylamino - 1:1 - diphenylpropan - 1 - ol (6.0 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 1, when 3 - dimethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, boiling point 192—3°C./18 mms. The hydrochloride prepared therefrom has melting point 168—170°C. (recrystallised from a mixture of ethanol and acetone).

3-Dimethylamino - 1:1 - diphenylprop-1 - ene (5.0 g.) is dissolved in ethanol (20 c.c.s.), 3% palladised charcoal (1.5 g.) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtrate by evaporation, and the residual oil fractionally distilled under reduced pressure. 3 - Dimethylamino-1:1-diphenylpropane distils at 183—185°C./16 mms., and crystallises on standing, melting point 44—45°C. (recrystallised from light petroleum).

EXAMPLE 3.

3-Diethylamino - 1:1 - diphenylpropan-1 - ol hydrochloride is dehydrated by the method described in Example 1. 3-Diethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 111°C./0.05 mms. The hydrochloride prepared therefrom has melting point 146—147°C. recrystallised from anhydrous acetone).

3 - Diethylamino - 1:1 - diphenylprop-1 - ene hydrochloride (6.0 g.) in ethanol (15 c.c.s) to which 3% palladised charcoal (2.0 g.) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino - 1:1 - diphenylpropane hydrochloride commences. The salt has melting point 145.5°C., and may be recrystallised from acetone.

EXAMPLE 4.

3 - N - Pyrrolidino - 1:1 - diphenylpropan - 1 - ol is dehydrated by the method described in Example 2. The product, 3-N-pyrrolidino - 1:1 - diphenylprop - 1-ene is obtained as a colourless oil, boiling point 125°C./0.02 mms., from which the hydrochloride, melting point 165—167°C. (recrystallised from a mixture of ethanol and ethyl acetate) is obtained.

The hydrochloride, when hydrogenated

by the method described in Example 3, yields 3-N-pyrrolidino - 1:1 - diphenylpropane hydrochloride of melting point 135—136°C. (recrystallised from a mixture of ethanol and ethyl acetate); the base obtained from the hydrochloride by treatment with aqueous alkali, has boiling point 125°C./0.02 mms.

EXAMPLE 5.

3-N-Morpholino - 1:1 - diphenylpropan - 1 - ol (6 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water and basified by addition of excess aqueous ammonia. The oil which separates crystallises on standing, and is removed by filtration and is washed with water. After crystallisation from ethanol, the product 3-N-morpholino - 1:1-diphenylprop-1-ene has melting point 70—72°C.; the hydrochloride prepared therefrom has melting point 218—219°C. (recrystallised from ethanol).

The hydrogenation of the hydrochloride, carried out using platinum oxide catalyst as described in Example 1 yields 3-N-morpholino - 1:1 - diphenylpropane hydrochloride, melting point 208—209°C. (recrystallised from a mixture of ethanol and ethyl acetate).

EXAMPLE 6.

Dehydration of 3-dimethylamino - 1:1-diphenylbutan - 1 - ol hydrochloride in a similar manner to that described in Example 1 yields 3-dimethylamino - 1:1-diphenylbut - 1 - ene, boiling point 194—196°C./19 mms., hydrochloride, melting point 160—161°C. (recrystallised from ethyl acetate). Hydrogenation is effected by shaking a solution of the hydrochloride (4.0 g.) in ethanol (20 c.c.s) with 3% palladised charcoal (2.0 g.) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3 - dimethylamino - 1:1 - diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176°C./12 mms. The hydrochloride obtained therefrom has melting point 157—158°C.

EXAMPLE 7.

3-Diethylamino - 1:1 - di - *p* - tolylpropan - 1 - ol hydrochloride is dehydrated by the method described in Example 1, when 3 - diethylamino - 1:1 - di - *p*-tolylprop - 1 - ene is obtained as a colourless liquid, boiling point 146—150°C./0.3 mms. pressure. The hydrochloride prepared from the base has melting point 179—180°C. (recrystallised from anhydrous acetone).

Hydrogenation of the hydrochloride by the method described in Example 3 yields 3 - diethylamino - 1:1 - di - *p*-tolylpropane hydrochloride, melting point 136—138°C. (recrystallised from ethyl acetate).

EXAMPLE 8.

3-Diethylamino - 1 - *cyclo*hexyl - 1 phenylpropan - 1 - ol hydrochloride is dehydrated as described in Example 1, to give an unsaturated amine of boiling point 123—125°C./0.3 mms. pressure, from which the hydrochloride, melting point 157—160°C. (recrystallised from ethyl acetate) is obtained.

The hydrochloride when subjected to hydrogenation by the method described in Example 6, is converted into 3-diethylamino - 1 - *cyclo*hexyl - 1 - phenylpropane (boiling point 190—192°C./18 mms. pressure). The hydrochloride prepared therefrom has melting point 125—126°C. (recrystallised from ethyl acetate).

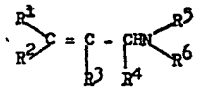
EXAMPLE 9.

Dehydration of 3 - diethylamino - 1-benzyl - 1 - phenylpropan - 1 - ol hydrochloride by the method described in Example 1 yields an unsaturated amine, which is obtained as a colourles oil on distillation under reduced pressure (boiling point 120—123°C./0.04 mms.). The hydrochloride obtained from the amine has melting point 157—159°C. after several recrystallisations from a mixture of ethanol and ethyl acetate.

Hydrogenation of the unsaturated amine by the method described in Example 2 yields 3 - diethylamino - 1-benzyl - 1 - phenylpropane, boiling point 112—114°C./0.02 mms. pressure, from which the hydrochloride, melting point 95—97°C. (recrystallised from ethyl acetate) is obtained.

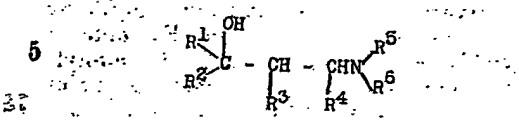
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the production of N-disubstituted - $\gamma\gamma$ - disubstituted allylamines of the formula



and salts thereof comprising the removal of the elements of water (by known methods for the conversion of tertiary

alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted - $\gamma\gamma$ - disubstituted - γ-hydroxy propylamines of the formula



in which the formulae R^1 and R^2 are aryl, aralkyl or cyclo-alkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions; R^1 and R^2 may be identical, provided that both are not aralkyl groups; R^3 is hydrogen or alkyl; R^4 is hydrogen, alkyl or aryl (optionally substituted as above); R^5 and R^6 are identical or different and are alkyl or aryl, or $-NR^5R^6$ may denote the piperidino-, pyrrolidino- or morpholino- groups.

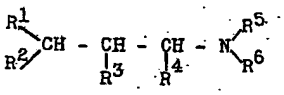
2. The process claimed in claim 1 wherein the substituted amino tertiary alcohol or a salt thereof is dissolved in a mixture of acetic acid and concentrated aqueous hydrochloric acid and the solution refluxed for a period of 15 minutes to one hour.

3. The process claimed in claim 1 or claim 2 wherein after dehydration of the tertiary alcohol the solution contained in the product is evaporated to dryness under reduced pressure, the residue is dissolved in water, excess of an alkali such as concentrated ammonia is added, and the liberated base is separated by extraction with an organic solvent such as ether.

4. The process claimed in claim 3 wherein the liberated base is recovered by evaporation of the solvent and distillation under reduced pressure or if the base is solid by recrystallisation from a solvent.

5. The process claimed in claim 3 wherein the base is converted into its hydrochloride by treating the dried solution of the base in a non-aqueous solvent with dry hydrogen chloride, thereby precipitating the base in the form of its hydrochloride and separating the latter from the solution.

6. The process claimed in claim 1 wherein the substituted allylamines prepared in accordance therewith are converted into N-disubstituted - $\gamma\gamma$ - disubstituted propylamines of the formula



(wherein R^1, R^2, R^3, R^4, R^5 and R^6 have the same meaning as above) by reduction under mild conditions.

7. The process claimed in claim 6 wherein the reduction is carried out upon the base or its hydrochloride dissolved in water, ethyl alcohol or other solvent by the action of hydrogen in the presence of a hydrogenation catalyst.

8. The process claimed in claim 7 wherein the reduction is carried out at atmospheric pressure and the hydrogenation catalyst is platinum black or palladised charcoal.

9. The process of preparing N-disubstituted - $\gamma\gamma$ - disubstituted allylamines and N - disubstituted - $\gamma\gamma$ - disubstituted propylamines of the general formulæ hereinbefore given substantially as hereinbefore described in any of the Examples hereinbefore given.

10. N - disultituted - $\gamma\gamma$ - disubstituted allylamines and N - disubstituted - $\gamma\gamma$- disubstituted propylamines having the general formulae hereinbefore given when prepared by the process claimed in any preceding claim.

Dated this 3rd day of December, 1947.
G. H. FRAZER,
Chartered Patent Agent.

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PATENT SPECIFICATION

627,139

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Index at acceptance:—Class 2(iii), B4(a2: a4: d), C2a(2: 14: 19), C2b(2: 3), C3a13a3.

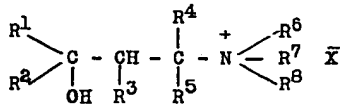
PROVISIONAL SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted-allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted - γ-hydroxypropylammonium salts, N-trisubstituted - γγ - disubstituted - allylammonium salts and N-trisubstituted-γγ-disubstituted-propylammonium salts of the general formula:—



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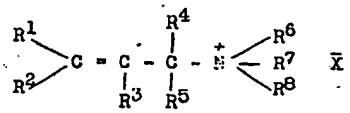

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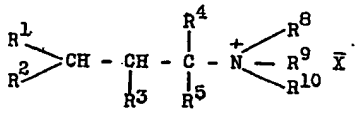


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

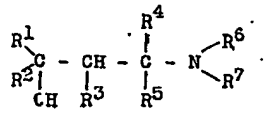
R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or—NR^9R^{10} may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups,

$\bar{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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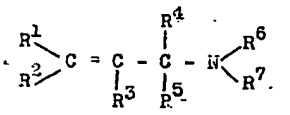

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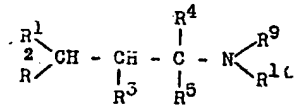


(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention, may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β-tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organomagnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted - allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ-hydroxy-propylamines of general formula (IIV (above). The N-disubstituted - $\gamma\gamma$ - disubstituted-propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents.

The following examples illustrate the invention:

EXAMPLE 1.

A solution of the ethyl ester of β-piperidinopropionic acid (37 parts by weight) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 2 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture which is cooled to 0° C., until acid to congo red. After standing for 1 hour at 0°C., the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 1:1-diphenyl-3-piperidinopropanol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropanol (1 part) is dissolved in anhydrous acetone (10 parts), methyl iodide (1 part) added and the mixture boiled under reflux for 15 minutes. On cooling N-methyl-3-hydroxy - 3:3 - diphenylpropylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C. (uncorrected).

EXAMPLE 2.

1:1-Diphenyl - 3 - dimethylaminopropanol is prepared from the ethyl ester of β - dimethylaminopropionic acid (29 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl - 3 - dimethylaminopropanol has melting point 167° C. (uncorrected) after recrystallisation from benzene or light petroleum.

1:1-Diphenyl - 3 - dimethylaminopropanol (4 parts) is dissolved in boiling ethyl alcohol (80 parts) and ethyl iodide (5 parts) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C. with decomposition (uncorrected) after recrystallisation from ethyl alcohol.

EXAMPLE 3.

1:1-Diphenyl - 3 - dimethylaminopropanol (2 parts) is dissolved in boiling ethyl alcohol (40 parts) and benzyl chloride (3 parts) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 parts) is gradually added, and the crystals of N-dimethyl-N-benzyl - 3 - hydroxy - 3:3 - diphenylpropylammonium chloride filtered off and recrystallised from ethyl alcohol; melting point 251° C. (uncorrected) with decomposition.

EXAMPLE 4.

1:1 - Diphenyl - 3 - diethylaminopropanol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1-Diphenyl-3-diethylaminopropanol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum has melting point 53° C. (uncorrected).

1:1 - Diphenyl - 3 - diethylaminopropanol (1 part) is dissolved in anhydrous acetone (2 parts), methyl iodide (1 part) in anhydrous acetone (2 parts) added and the mixture allowed to stand for 2 hours. N - Methyl-N-diethyl-3-hydroxy-3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C. (uncorrected).

EXAMPLE 5.

A solution of 1:1-diphenyl-3-piperidinopropanol (3 parts) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 parts) and glacial acetic acid (20 parts) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 1:1-diphenyl-3-piperidino-1:2-propene is collected as a colourless liquid, boiling point 138° C/0.1 mm. pressure.

1:1 - Diphenyl-3-piperidino-1:2-propene (1 part) is dissolved in anhydrous acetone (3 parts) and a solution of methyl iodide (1 part) in acetone (1 part) is added, when heat is developed. After standing for several hours, the crystals of N - methyl-3:3-diphenyl-allylpiperidinium iodide which separates are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C. (uncorrected) with decomposition.

EXAMPLE 6.

1:1-Diphenyl-3-piperidino - 1:2 - propene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C. (uncorrected).

1:1-Diphenyl-3-piperidino - 1:2 - propene hydrochloride (1 part) in ethyl alcohol (10 parts) is shaken at room temperature with platinum oxide (0.02 parts) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. I, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone, when 1:1 - diphenyl-3-piperidinopropane hydrochloric is obtained as crystals; melting point 215—217° C. (uncorrected). The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 1:1-diphenyl-3-piperidinopropane; melting point 39—40° C. (uncorrected).

1:1-Diphenyl-3-piperidinopropane (1 part) is dissolved in anhydrous acetone (2 parts) and methyl iodide (1 part) in anhydrous acetone (1 part) is added. After standing for 2 hours the crystals of N - methyl - 3:3 - diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C. (uncorrected) with decomposition.

EXAMPLE 7.

1:1 - Diphenyl-3-diallylaminopropanol is prepared from the ethyl ester of β-diallylaminopropionic acid (39 parts) and the Grignard reagent made from bromobenzene (110 parts) and magnesium (17 parts) by a method essentially similar to that described in Example 1 (above) for the preparation of 1:1-diphenyl-3-piperidinopropanol. 1:1 - Diphenyl-3-diallylaminopropanol has boiling point 157—159° C/0.4 mm. and melting point 25—27° C. (uncorrected) after recrystallisation from light petroleum (boiling point 40—60° C).

1:1 - Diphenyl - 3 - diallylaminopro-

panol (3 parts) is dissolved in anhydrous acetone (5 parts) and methyl iodide (2 parts) added to the solution. The fine needles of N - methyl - N - diallyl-3-hydroxy - 3:3 - diphenylpropylammonium iodide which quickly separate, are recrystallised from aqueous ethyl alcohol; melting point 196—197° C. with decomposition (uncorrected).

EXAMPLE 8.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene is prepared from 1:1-diphenyl-3-diallylaminopropanol by dehydration by a method essentially similar to that described in Example 5 for the preparation of 1:1-diphenyl-3-piperidinol-:2-propene. 1:1-Diphenyl-3-diallylamino-1:2-propene is obtained as a colourless oil, boiling point 134° C/0.2 mm. by distillation under reduced pressure.

1:1 - Diphenyl - 3 - diallylamino-1:2-propene (2 parts) is dissolved in anhydrous acetone (3 parts), methyl iodide (2 parts) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N - methyl-N-diallyl-3:3-diphenylallylammonium iodide are separated by filtration and recrystallised from ethyl alcohol; melting point 149—151° C. (uncorrected) with decomposition.

Dated this 28th day of May, 1947.

THE WELLCOME FOUNDATION LTD.,
A. N. FALDER,
Secretary.

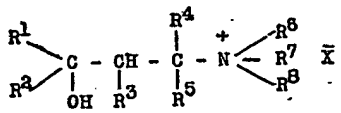
COMPLETE SPECIFICATION

Improvements in and relating to the Preparation of Quaternary Ammonium Salts of Substituted Propanolamines, Allylamines and Propylamines

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company, and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to a process for the preparation of new derivatives of substituted γ-hydroxypropylamines, substituted allylamines and substituted propylamines, and has for its object the preparation of certain novel and useful compounds, namely quaternary ammonium salts derived from γγ-disubstituted-γ-hydroxypropylamines, γγ-disubstituted allylamines and γγ-disubstituted propylamines. No claim is made herein to the aforesaid compounds from which the novel quaternary ammonium salts to which our invention relates are derived.

According to our invention we prepare N - trisubstituted - γγ - disubstituted-γ-hydroxypropylammonium salts and N-trisubstitued - γγ - disubstituted-propylammonium salts of the general formula:—



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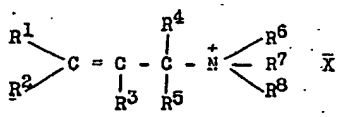

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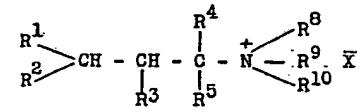


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical

R^4 denotes hydrogen or an alkyl radical

R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino- or piperidino-group, optionally substituted by one or more alkyl groups,

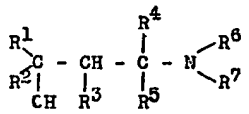
R^8 denotes an alkyl or aralkyl radical

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralkyl radicals, or $—NR^9R^{10}$

may denote the pyrrolidino-, morpholino-, or piperidino-group, optionally substituted by one or more alkyl groups, and

$\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical.

In accordance with our invention, these quaternary salts are made by treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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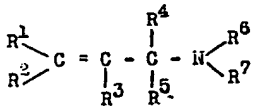

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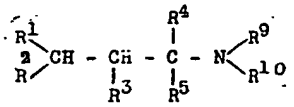


(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

The quaternisation, in accordance with our invention may be effected in a solvent (such as anhydrous acetone, ethyl alcohol, dioxan) at room temperature or at the boiling point of the solvent or at intermediate temperatures. Preferably an excess of the quaternising agent is employed. The solvent and the quantity used is preferably so selected that the quaternary salt crystallises from the reaction mixture on cooling. In cases when this cannot conveniently be done, a liquid in which the quaternary salt is insoluble (such as ether) is added gradually to the reaction product until crystallisation commences.

The N-disubstituted-$\gamma\gamma$-disubstituted-γ-hydroxypropylamines of general formula (IV) (above) may be prepared by bringing about a Grignard reaction between the appropriate β - tertiaryaminopropionic acid alkyl ester and an appropriate organo-magnesium halide and subsequently hydrolysing the organo-magnesium compound so produced, or alternatively they may be made by bringing about a Grignard reaction between the appropriate β-tertiaryaminoethyl aryl ketone and an appropriate organomagnesium halide, and subsequently hydrolysing the organiomagnesium compound so produced. The N-disubstituted-$\gamma\gamma$-disubstituted-allylamines of general formula (V) (above) are prepared by removal of the elements of water from the corresponding γ - hydroxy - propylamines of general formula (IV) (above). The N-disubstituted - $\gamma\gamma$ - disubstituted - propylamines of general formula (VI) (above) are prepared by reduction of the corresponding allylamines of general formula (V) (above).

The new quaternary salts to which this invention relates are crystalline compounds, soluble in water. They are useful as therapeutic agents having antispasmodic and broncho-dilating action.

The following examples illustrate the invention:—

EXAMPLE I.

A solution of the ethyl ester of β-piperidino-propionic acid (37 grams) in dry ether is added gradually to an ether solution of the Grignard reagent made from bromobenzene (110 cubic centimetres) and magnesium (17 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour, the reaction mixture is heated under reflux for 3 hours and is then cooled to 0° C. and stirred into crushed ice. Concentrated hydrochloric acid is then gradually added to the stirred mixture, cooled to 0° C., until acid to congo red. After standing for 1 hour at 0° C. the salt which separates is filtered off and washed with ether. The salt is suspended in chloroform and the suspension shaken with excess of concentrated ammonia solution and the chloroform layer separated, washed with water and dried. The chloroform is evaporated, leaving 3-N-piperidino-1:1-diphenylpropan-1-ol as a solid residue, which after recrystallisation from benzene or light petroleum, forms crystals which melt at 120—121° C.

3 - N - Piperidino - 1:1 - diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (10 cubic centimetres), methyl iodide (1 gram) added and the mixture boiled under reflux for 15 minutes. On cooling N - methyl - 3-hydroxy-3:3-diphenyl - propylpiperidinium iodide crystallises out and after recrystallisation from alcohol has melting point 214—215° C.

EXAMPLE 2.

A solution of 3 - piperidino - 1 : 1-diphenylpropan-1-ol (3 grams) (prepared as described in Example 1) in concentrated aqueous hydrochloric acid (6 cubic centimetres) and glacial acetic acid (20 cubic centimetres) is boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure and the residual solid is dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ethereal solution is dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product, 3-N-piperidino-1 : 1-diphenylprop-1-ene, is collected as a colourless liquid, boiling point 138° C./at 0.1 mm. pressure.

3 - N-Piperidino-1 : 1-diphenylprop-1-ene (1 gram) is dissolved in anhydrous acetone (3 cubic centimetres) and a solution of methyl iodide (1 gram) in acetone (1 cubic centimetre) is added, when heat is developed. After standing for several hours, the crystals of N-methyl-3 : 3-diphenylprop - 2 - enylpiperidinium iodide which separate are removed by filtration and recrystallised from ethyl alcohol, melting point 189—190° C., with decomposition.

EXAMPLE 3.

3 - N - Piperidino-1 : 1-diphenylprop-1-ene is converted to the hydrochloride by passing dry hydrogen chloride into a chloroform solution until acid to congo red and adding ether until crystallisation commences. The hydrochloride is then removed by filtration and recrystallised from a mixture of chloroform and acetone, melting point 209—210° C.

3-N-Piperidino - 1 : 1 - diphenylprop-1-ene hydrochloride (1 gram) in ethyl alcohol (10 cubic centimetres) is shaken at room temperature with platinum oxide (0.02 grams) (prepared according to the directions given in Organic Syntheses, 1932, Collective Vol. 1, *p. 452*) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the alcohol is removed by evaporation under reduced pressure. The residue is recrystallised from a mixture of alcohol and acetone when 3-N-piperidino-1 : 1-diphenylpropane hydrochloride is obtained as crystals, melting point 215—217° C. The free base is obtained by suspending the hydrochloride in water, adding excess aqueous ammonia and extracting with ether. The ethereal extract, after drying and evaporation of ether, yields crystals of 3-N-piperidino-1 : 1-diphenylpropane, melting point 40—41° C.

3 - N - Piperidino - 1 : 1 - diphenylpropane (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres) and methyl iodide (1 gram) in anhydrous acetone (1 cubic centimetre) is added. After standing for 2 hours the crystals of N-methyl-3 : 3-diphenylpropylpiperidinium iodide are filtered off and recrystallised from ethyl alcohol; melting point 175—176° C., with decomposition.

EXAMPLE 4.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol is prepared from the ethyl ester of β-dimethylaminopropionic acid (29 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N - piperidino-1 : 1-diphenylpropan-1-ol 3 - Dimethylamino-1 : 1-diphenylpropan-1-ol has melting point 166° C. after recrystallisation from benzene or light petroleum.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (4 grams) is dissolved in boiling ethyl alcohol (80 cubic centimetres) and ethyl iodide (5 grams) added and the mixture boiled under reflux for 2 hours. On cooling N-dimethyl-N-ethyl-3-hydroxy-3 : 3 - diphenylpropylammonium iodide crystallises out and melts at 200—201° C., with decomposition, after recrystallisation from ethyl alchohol.

EXAMPLE 5.

N - Dimethyl - N - propyl-3-hydroxy-3 : 3 - diphenylpropylammonium bromide similarly is prepared by boiling 3-dimethylamino - 1 : 1 - diphenylpropan-1-ol with 1-bromo-propane in ethanolic solution for 5 hours (under reflux). The product melts with decomposition at 231—233° C.

EXAMPLE 6.

N - Dimethyl-N-butyl-3-hydroxy-3 : 3-diphenylpropylammonium bromide is prepared from 3 - dimethylamino-1 : 1-diphenylpropan-1-ol and 1-bromobutane in a similar manner to that described in Example 5. It has melting point 233—235° C. (with decomposition).

EXAMPLE 7.

3-Dimethylamino - 1 : 1 - diphenylpropan-1-ol (2 grams) is dissolved in boiling ethyl alcohol (40 cubic centimetres) and benzyl chloride (3 grams) added, and the mixture boiled under reflux for 2 hours. The mixture is cooled, ether (50 cubic centimetres) is gradually added and the crystals of N - dimethyl - N - benzyl-3-hydroxy - 3 : 3 - diphenylpropylammonium chloride filtered off and recrystal-

lised from ethyl alcohol; melting point 251° C., with decomposition.

EXAMPLE 8.

3-Dimethylamino - 1:1 - diphenylpropan-1-ol (6.0 grams) is dissolved in concentrated hydrochloric acid (18 cubic centimetres) and glacial acetic acid (60 cubic centimetres) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 2, when 3-dimethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, boiling point 102—3° C./18 mm.

The methiodide (N - trimethyl - 3:3-diphenylprop-2-enylammonium iodide) is prepared by the method described in Example 2. It melts with decomposition at 203—205° C., after recrystallisation from ethanol.

EXAMPLE 9.

3 - Dimethylamino-1:1-diphenylprop-1-ene (5.0 grams) is dissolved in ethanol (20 cubic centimetres), 3% palladised charcoal (1.5 grams) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtration by evaporation, and the residual oil fractionally distilled under reduced pressure. 3-Dimethylamino - 1:1 - diphenylpropane distils at 183—185° C./16 mm., and crystallises on standing, melting point 44—45° C. (recrystallised from light petroleum).

3-Dimethylamino - 1:1 - diphenylpropane (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. Heat is developed and crystals of N-trimethyl 2:3-diphenylpropylammonium iodide separate. The crystals are filtered off and recrystallised from a mixture of methanol and ethyl acetate; melting point 179—180° C.

EXAMPLE 10.

3 - Diethylamino-1:1-diphenylpropan-1-ol is prepared from the ethyl ester of β-diethylaminopropionic acid (35 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 (above) for the preparation of 3-N-piperidino - 1:1 - diphenylpropan - 1 - ol. 3-Diethylamino - 1:1 - diphenylpropan-1-ol, purified by distillation under reduced pressure (boiling point 154° C/0.2 mm.) or by recrystallisation from light petroleum, has melting point 53.5° C.

3 - Diethylamino-1:1-diphenylpropan-1-ol (1 gram) is dissolved in anhydrous acetone (2 cubic centimetres), methyl iodide (1 gram) in anhydrous acetone (2 cubic centimetres) added, and the mixture allowed to stand for 2 hours. N-Methyl-N-diethyl - 3 - hydroxy - 3:3-diphenylpropylammonium iodide, which crystallises out, is recrystallised from methyl alcohol and has melting point 198—199° C.

EXAMPLE 11.

3 - Diethylamino-1:1-diphenylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2. 3-Diethylamino-1:1-diphenylprop-1-ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 110° C./0.05 mm. The hydrochloride prepared therefrom has melting point 146—147° C. (recrystallised from anhydrous acetone).

The tertiary amine (3.0 grams) is dissolved in acetone (5.0 cubic centimetres) and methyl iodide (3.0 grams) in acetone (2 cubic centimetres) gradually added with cooling. The crystalline precipitate of N-methyl-N-diethyl - 3:3 - diphenylprop-2-enylammonium iodide is removed and recrystallised from methanol. It has a melting point of 185—186° C.

EXAMPLE 12.

3-Diethylamino - 1:1 - diphenylprop-1-ene hydrochloride (6.0 grams) in ethanol (15 cubic centimetres) to which 3% palladised charcoal (2.0 grams) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (after approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino-1:1-diphenylpropane hydrochloride commences. The salt has melting point 145.5° C. and may be recrystallised from acetone. The free base (obtained as a colourless liquid) is converted to the quaternary methiodide (N - methyl - N-diethyl - 3:3 - diphenylpropylammonium iodide) of melting point 162—163° C. (recrystallised from aqueous ethanol) by the method described in Example 2.

EXAMPLE 13.

Ethyl β - di-*n*-propylaminopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume 67, page 1071) (40.2 grams) in anhydrous ether (50 cubic centimetres) treated with the Grignard reagent made from bromobenzene ((110 grams) and magnesium (17 grams) under the conditions described in Example 1, yields 3-di-*n*-propylamino - 1:1 - diphenylpropan-1-ol which is purified by fractional distillation under reduced pressure (boiling point 153—154° C. at 0.1 mm.) and by recrystallisation from light petroleum; the base has melting point 52.5—53.5° C.

The methiodide (N-methyl-N-dipropyl-3:3-diphenyl - 3 - hydroxypropylammo-

nium iodide) prepared therefrom by the method described in Example 2 has melting point 181—183° C., after recrystallisation from aqueous ethanol.

EXAMPLE 14.

Ethyl β-N-phenyl-N-methylaminopropionate (41.4 grams) in ether (100 cubic centimetres), treated with the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) in ether (200 cubic centimetres) in a similar manner to that described in Example 1, yields 3-N-phenyl-N methylamino-1:1-diphenylpropan-1-ol, melting point 97° C. (recrystallised from ethanol). The ethyl β-N-phenyl - N - methylaminopropionate used as starting material is prepared by a method essentially similar to that described by Elderfield, Gensler, Bembry, Kremer, Brody, Hageman and Head, *Journal of the American Chemical Society*, 1946, Volume *68*, page 1259, for the preparation of β-arylaminopropionic esters.

A mixture of ethyl acrylate (40g.), methylaniline (42.8 grams) and acetic acid (10 grams) is boiled under reflux for 12 hours, cooled, and taken up in an equal volume of ether. The ethereal solution is then washed with water, then with aqueous sodium bicarbonate solution and finally with water. The ethereal solution is then dried with anhydrous sodium sulphate, the ether evaporated, and the residual oil fractionally distilled under reduced pressure. The required ester is collected at 98—100° C/0.05 mm.

3-N-Phenyl - N - methylamino - 1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in ethanol (5.0 c.c.), methyl iodide (2.0 grams) added and the mixture allowed to stand for 24 hours. The N-dimethyl-N-phenyl - 3:3 - diphenyl-3-hydroxypropylammonium iodide which separates melts with decomposition at 176° C., after recrystallisation from aqueous ethanol.

EXAMPLE 15.

Ethyl - β - N - methyl-N-β-phenylisopropylaminopropionate (49.8 grams) in ether (100 cubic centimetres) is added dropwise to an ethereal solution of the Grignard reagent prepared from bromobenzene (110 grams) and magnesium (17 grams) and the mixture boiled under reflux for 2 hours. The cooled mixture is then poured on to crushed ice (100 grams) and acidified to congo red by the gradual addition of hydrochloric acid (concentrated). A gum, which rapidly solidifies, is precipitated, separated by filtration and washed with ether. The solid is then suspended in water (100 cubic centimetres) and chloroform (100 cubic centimetres) excess aqueous ammonia added with shaking, and the chloroform layer separated and dried over anhydrous sodium sulphate. Dry hydrogen chloride is then passed into the filtered chloroform solution until acid to congo red and other added to the point of crystallisation. 3-N-Methyl-N-2¹-phenyl-1¹-methylethylamino - 1:1 - diphenylpropan-1-ol hydrochloride separates and has melting point 207—208° C. after recrystallisation from aqueous ethanol; the base, liberated from the hydrochloride by addition of aqueous alkali, is a viscous oil.

The ethyl-β-N-methyl-N-β-phenyl*iso*propylminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenylisopropylaminopropionate used as starting material is prepared by allowing a mixture of ethyl acrylate (40 grams) and β-phenyl*iso*propylmethylamine (60 grams) to stand for 48 hours, then boiling under reflux for 4 hours and subsequently fractionally distilling the product under reduced pressure (boiling point 165—166° C./12 mm.).

The methiodide of the base is prepared by mixing with methyl iodide in acetone solution as described in Example 2. The product melts with decomposition at 226° C.

EXAMPLE 16.

Ethyl β-N-pyrolidinopropionate when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-pyrrolidino-1:1-diphenyl-propan-1-ol melting point 171—172° C. (recrystallised from ethyl acetate).

The ethyl β-N-pyrrolidinopropionate is prepared by mixing pyrrolidine (21 grams) with ethyl acrylate (30 grams) and allowing to stand at room temperature for several days. The product is distilled under reduced pressure, the required ester being collected at 108—110° C./23 mm.

3 - N - Pyrrolidino-1:1-diphenylpropan-1-ol (2.0 grams) is dissolved in chloroform (25 cubic centimetres), methyl iodide (2.0 grams) added, and the mixture allowed to stand for 24 hours. The crystals of N-methyl-3:3-diphenyl-3-hydroxypropylpyrrolidinium iodide which separate are recrystallised from methanol; melting point 210° C.

EXAMPLE 17.

Ethyl β-N-morpholinopropionate (prepared as described by Weisel, Taylor, Mosher and Whitmore, *Journal of the American Chemical Society*, 1945, Volume *67*, page 1071,) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-N-

morpholino-1:1-dihpenylpropan - 1 - ol melting point 106° C. (recrystallised from light petroleum).

The corresponding methiodide is prepared by the method described in Example 1; it melts with decomposition at 203—204° C.

EXAMPLE 18.

3 - Diallylamino-1:1-diphenylpropan-1-ol is prepared from ethyl β-diallylaminopropionate (39 grams) and the Grignard reagent made from bromobenzene (110 grams) and magnesium (17 grams) by a method essentially similar to that described in Example 1 for the preparation of 3-N-piperidino-1:1-diphenyl-propan-1-ol. The product has boiling point 157—159° C./0.4 mm. after recrystallisation from light petroleum.

3 - Diallylamino-1:1-diphenylpropan-1-ol (3 grams) is dissolved in anhydrous acetone (5 cubic centimetres) and methiodide (2 grams) added to the solution. The fine needles of N-methyl-N-diallyl-3:3 - diphenyl-3-hydroxypropyl - ammonium iodide which quickly separate are recrystallised from aqueous methyl alcohol; melting point 196—197° C., with decomposition.

EXAMPLE 19.

3 - Diallylamino-1:1-diphenylprop-1-ene is prepared from 3-diallylamino-1:1-diphenylpropan-1-ol by dehydration by a method essentially similar to that described in Example 2 for the preparation of 3-piperidino-1:1-diphenyl-prop-1-ene. The product is a colourless oil, of boiling point 134° C./0.2 mm.

3 - Diallylamino-1:1-diphenylprop-1-ene (2 grams) is dissolved in anhydrous acetone (3 cubic centimetres), methyl iodide (2 grams) added and the mixture heated under reflux for 1 hour. After cooling and standing for 24 hours, the crystals of N-methyl-N-diallyl-3:3-diphenylprop-2-enylammonium iodide are separated by filtration and recrystallised from ethanol, melting point 149—151° C. with decomposition.

EXAMPLE 20.

Ethyl β-dimethylaminobutyrate (prepared as described by Breckpot, Bulletin Societe Chimique de Belgique 1923, volume *32*, page 412) when treated with the Grignard reagent prepared from bromobenzene by the same method as that described in Example 1 yields 3-dimethylamino - 1:1-diphenyl-butan-1-ol melting point 125—126° C. (recrystallised from aqueous ethanol). The tertiary amine (2.0 grams) is dissolved in warm acetone (10 cubic centimetres), methyl iodide (2.0 grams) added and the mixture boiled under reflux for 15 minutes. On cooling and standing, the corresponding morpholino-1:1-diphenylpropan - 1 - ol ing point 251° C. after recrystallisation from aqueous ethanol.

EXAMPLE 21.

Dehydration of 3-dimethylamino-1:1-diphenylbutan-1-ol hydrochloride in a similar manner to that described in Example 2 yields 3-dimethylamino-1:1-diphenylbut-1-ene, boiling point 194—196° C./19 mm., (hydrochloride, melting point 160—161° C.)

The methiodide prepared therefrom by the method described in Example 2 melts with decomposition at 210—212° C. after recrystallisation from aqueous ethanol.

EXAMPLE 22.

Hydrogenation of 3-dimethylamino-1:1-diphenylbut-1-ene hydrochloride (4.0 grams) is effected by shaking in ethanol (20 cubic centimetres) with 3% palladised charcoal (2.0 grams) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3-dimethylamino-1:1-diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176° C./12 mm.

The methiodide prepared therefrom by the method described in Example 2 has melting point 204—205° C. after recrystallisation from ethanol.

EXAMPLE 23.

Ethyl β - diethylaminopropionate (26 grams) in anhydrous ether (50 c.c.) is added dropwise to an ether solution of the Grignard reagent made from *p*-bromotoluene (90 grams) and magnesium (12.8 grams), stirred and cooled in a bath kept at 0° C. After stirring in the cold for 1 hour and boiling under reflux for 2 hours, the reaction mixture is worked up as described in Example 1. The 3-diethylamino-1:1-di - *p* - tolylpropan - 1 - ol so obtained is purified by fractional distillation under reduced presure (boiling point 160—162° C./0.5 mm.) and may be recrystallised from a small volume of light petroleum, melting point 56—58° C.

The methiodide prepared therefrom (method described in Example 2) has melting point 188—189° C. (may be recrystallised from aqueous ethanol).

EXAMPLE 24.

3 - Diethylamino-1:1-di-*p*-tolylpropan-1-ol hydrochloride is dehydrated by the method described in Example 2, when 3-diethylamino-1:1-di-*p*-tolylprop-1-ene is obtained as a colourless liquid, boiling point 146—150° C./0.3 mm. pressure.

The tertiary base (1.5 grams) in methanol (3 cubic centimetres) is mixed with methyl iodide (1.5 grams) when heat is developed. After standing for several hours, anhydrous ether is added dropwise with stirring until precipitation of the methiodide is complete. N-Methyl-N-diethyl-3:3-di-*p*-tolylprop-2-enyl-ammonium iodide melts with decomposition at 141—143° C. after recrystallisation from a mixture of ethyl acetate and ethanol.

EXAMPLE 25.

3-Diethylamino-1:1-di-*p*-tolylprop-1-ene hydrochloride (melting point 179—180° C.; which was obtained from the base described in Example 24) when hydrogenated by the method described in Example 3, yields 3-diethylamino-1:1-di-*p*-tolylpropane hydrochloride, melting point 136—138° C. (recrystallised from methyl acetate) from which the base is obtained as an oil.

The methiodide prepared from the tertiary amine, as described in Example 2, has melting point 169—170° C. after recrystallisation from ethanol.

EXAMPLE 26.

β-Diethylaminopropiophenone hydrochloride (prepared as described by Blicke and Burckhalter, *Journal of the American Chemical Society*, 1942, Volume *64*, page 451) (48.3 grams) is added in small portions to the Grignard reagent prepared from benzyl chloride (76 grams) and magnesium (14.6 grams) in ether (100 cubic centimetres), stirred and cooled to 0° C. The reaction and working up of the product is then carried out as described in Example 1. 4-Diethylamino-1:2-diphenylbutan-2-ol is obtained as crystals, melting point 54—55° C. (recrystallised from light petroleum).

The methiodide prepared therefrom by the method described in Example 2, has melting point 197—198° C. after recrystallisation from methanol.

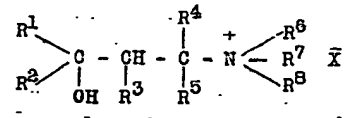
EXAMPLE 27.

β-Diethylaminopropionphenone hydrochloride (48.3 grams) is added in small portions to the Grignard reagent prepared from *cyclo*hexyl bromide (98 grams) and magnesium (14.6 grams) in 100 c.c ether stirred and cooled to 0° C. After boiling under reflux for 12 hours the product is worked up by a similar method to that described in Example 1. 3-Diethylamino-1-*cyclo*hexyl-1-phenylpropan-1-ol is purified by distillation under reduced pressure (boiling point 132—135° C./0.02 mm.) and by recrystallisation from light petroleum (melting point 50.5—52° C.).

The tertiary base (1.0 gram) is dissolved in acetone (3 cubic centimetres) and methyl iodide (1.0 gram) added. After standing for several hours, crystallisation of the product is completed by gradual addition of anhydrous ether N-Methyl-N-diethyl-3-*cyclo*hexyl-3-phenyl-3-hydroxypropylammonium iodide has melting point 160—162° C. after recrystallisation from ethyl acetate and ethanol.

Having now particularly described and ascertained the nature of our said invention, and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the preparation of N-trisubstituted-γγ-disubstituted-γ-hydroxypropylammonium salts, N-trisubstituted-γγ-disubstituted-allylammonium salts and N-trisubstituted-γγ-disubstituted-propylammonium salts of the general formula:—



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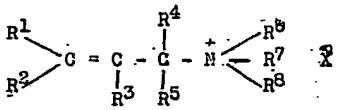

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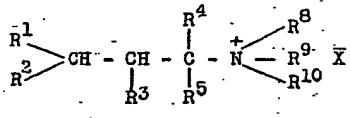


(III)

wherein R^1 and R^2 may be either identical or different and denote aryl, aralkyl or *cyclo*alkyl radicals, optionally substituted, for example, by alkyl or alkoxy groups,

R^3 denotes hydrogen or an alkyl radical,

R^4 denotes hydrogen or an alkyl radical,

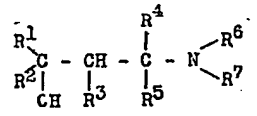
R^5 denotes hydrogen or an alkyl, aryl or aralkyl radical.

R^6 and R^7 may be either identical or different and denote alkyl, alkenyl, *cyclo*alkyl, aryl or aralkyl groups, or $—NR^6R^7$ may denote the pyrrolidino-, morpholino, or piperidino-group, optionally substituted by one or more alkyl groups,

R^8 denotes an alkyl or aralkyl radical,

R^9 and R^{10} may be either identical or different and denote alkyl, *cyclo*alkyl, aryl or aralykyl radicals, or $—NR^9R^{10}$ may denote the pyrrolidino-, morpho-

lino-, or piperidino-group, optionally substituted by one or more alkyl groups, and $\overline{X}$ is an acid radical such as chloride, bromide, iodide or methosulphate radical, comprising treating an alkyl or aralkyl halide or other reactive acid salt R^8X with a tertiary amine of the general formula



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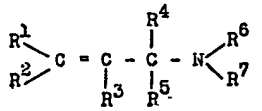

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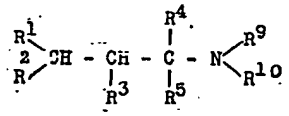

(VI)

(wherein R^1, R^2, R^3, R^4, R^5, R^6 R^7, R^9 and R^{10} have the same meaning as above) or *vice versa*.

2. The process claimed in claim 1 in which an excess of the reactive acid salt R^8X is present during the reaction.

3. The process claimed in claim 1 in which a solvent for both reactants is present during the reaction and the reaction is carried out at room temperature or at the boiling point of the solvent or at some intermediate temperature.

4. The process claimed in claim 3 in which the solvent is so selected and is present in such quantity that the desired quaternary salt crystallizes from the reaction mixture on cooling the latter.

5. The process claimed in claim 3 in which a liquid in which the reaction product is insoluble is added gradually to the reaction mixture after the reaction has been completed, until crystallization of the reaction product occurs.

6. The process claimed in claim 3 in which the solvent employed is anhydrous acetone, ethyl alcohol or dioxan.

7. A process for preparing compounds having the general formulae I, II or III given in claim 1, substantially as hereinbefore described.

8. A process for preparing a chemical compound having a formula within the scope of the general formulae I, II or III given in claim 1, substantially as described in any one of the Examples hereinbefore given.

9. A chemical compound when prepared by the process claimed in any preceding claim.

Dated this 7th day of May, 1948.

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(54) Title: TRANSDERMAL ADMINISTRATION OF OXYBUTYNIN

(57) Abstract

The present invention is directed to the transdermal administration of oxybutynin together with a suitable permeation enhancer. The invention includes a transdermal drug delivery device comprising a matrix adapted to be placed in oxybutynin- and permeation enhancer-transmitting relation with the skin site. The matrix contains sufficient amounts of a permeation enhancer and of oxybutynin, in combination, to continuously administer to the skin for a predetermined period of time the oxybutynin to provide an effective therapeutic result. The invention is also directed to a method for the transdermal administration of a therapeutically effective amount of oxybutynin together with a skin permeation-enhancing amount of a suitable permeation enhancer.

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TRANSDERMAL ADMINISTRATION OF OXYBUTYNIN

FIELD OF THE INVENTION

This invention relates the efficacious and safe, controlled transdermal administration of oxybutynin and related compounds for the treatment of neurogenic bladder disorders.

BACKGROUND OF THE INVENTION

Neurogenic bladder disease is a disorder involving loss of control of urination. The major symptoms of this disease are urinary frequency, urinary retention or incontinence. There are two types of lesions that cause a neurogenic bladder. The first, upper motoneuron lesion, leads to hypertonia and hyperreflexia of the bladder, a spastic condition, giving rise to symptoms of urinary frequency and incontinence. The second lesion, a lower motoneuron lesion, involves hypotonia and hyporeflexia of the bladder. The major symptoms in this condition are urinary retention, since the voiding reflex has been lost, and incontinence, which occurs when the bladder "leaks", being full to overflowing.

The majority of neurogenic bladder patients have the spastic or hypertonic bladder. The clinician usually attempts to convert the condition of hyperreflexia and hypertonia to hypotonia, thereby treating the primary problem of incontinence. When the condition has been converted to hypotonia, it can be managed by intermittent catheterization. However, there is a significant population of patients who cannot be converted completely from the hypertonic to the hypotonic condition, and who still find they have to urinate every hour or are incontinent. For these patients, treatment with an anticholinergic drug is necessary. The drug of choice is oxybutynin (4-diethylamino-2-butynylphenylcyclohexylglycolate).

The use of oxybutynin chloride, as approved by the FDA in the United States, is described in the 1992 Physician's Desk Reference, pages 1332 through 1333 with reference to the drug Ditropan® manufactured by Marion Merrell Dow. Oxybutynin is normally administered to human beings orally at relatively high doses (5 mg

tablets taken two to four times a day). Oxybutynin has been incorporated into tablets, capsules, granules or pills containing 1-5 mg, preferably 5 mg, of oxybutynin chloride, syrups containing 1-5 mg, preferably 5 mg, of oxybutynin chloride per 5 ml and transdermal compositions (creams or ointments) containing 1-10 weight percent ("wt %") oxybutynin chloride. See, BE 902605.

In U.S. Patent No. 4,747,845, oxybutynin was listed as an agent that could be incorporated into a transdermal synthetic resin matrix system for extended duration drug release, but oxybutynin was not used in the device. In U.S. Patent No. 4,928,680 oxybutynin was given as a pharmacologically active agent suitable for transdermal delivery, but as with the above reference, oxybutynin was not incorporated into the device.

Oxybutynin has been incorporated into a device having a water impermeable barrier layer, a reservoir containing oxybutynin in contact with the inner surface of the barrier layer and a removable protector layer in contact with the other surface of the reservoir. The reservoir is a polyurethane fiber mat impregnated with an aqueous solution containing 25 mg/ml of oxybutynin. The device was placed on a 20 μm thick polybutadiene film. The non-device carrying surface was in contact with 0.05 M isotonic phosphate buffer solution. The *in vitro* release rate measured was approximately 12 mg over 24 hours through a 49 cm^2 area or 10 $\mu g/cm^2/hr$. (U.S. Patent No. 4,784,857 and EP 0 250 125).

In Pharm Res, "Development of Transdermal Delivery Systems of Oxybutynin: In-Vivo Bioavailability", P. Keshary *et al.*, (NY)8 (10 Supp) 1991, p. S205 three types of transdermal delivery systems, using matrix-diffusion controlled and membrane-permeation controlled technologies were discussed. The *in vitro* permeation rate of about 9, 12 and 12 $\mu g/cm^2/hr$ and *in vitro* release rates (sink condition) of about 1160, 402 and 57.2 $\mu g/cm^2/hr$ were obtained from Silastic monolithic, acrylic pressure sensitive adhesive matrix and reservoir type delivery systems, respectively. In humans, steady state plasma concentrations of about 1.86 ng/ml were obtained after 6 hours of

application of a single 20 cm^2 patch of the acrylic pressure sensitive adhesive matrix type.

The transdermal route of administration for drugs and other biologically active agents ("agents") has been proposed for a wide variety of systemically acting and locally acting agents on either a rate-controlled or non rate-controlled basis and is described in numerous technical publications and patents, such as U.S. Patents 3,598,122; 3,598,123; 3,731,683; 3,797,494; 4,031,894; 4,201,211; 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,588,580; 4,645,502; 4,704,282; 4,788,062; 4,816,258; 4,908,027; 4,943,435; and 5,004,610. The disclosures of the above patents are incorporated herein by reference.

Just as certain drugs can irritate, sensitize or be otherwise toxic, so can permeation enhancers. The use of permeation enhancers for transdermal administration is described in numerous technical publications and patents, such as U.S. Patents Nos. 4,940,586; 4,863,738; 4,820,720; 4,746,515; 4,568,343; 4,405,616; 4,379,454; 4,343,798; 4,335,115; 4,299,826; 4,130,667; 4,130,643; 4,046,886; British Patent No. 1,001,949 and Idson, Percutaneous Absorption, J. Phar. Sci., Vol. 64, No. 66, June 1975, pp. 901-924.

Permeation enhancers that are not normally toxic at the concentrations employed in cosmetic or medical compositions may exhibit toxic effects at the higher concentrations required to produce adequate permeation enhancement. No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.

Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many

potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.

The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system.

As used herein, the term "oxybutynin" is used to designate oxybutynin, acid addition salts of oxybutynin and the related compounds thereof. The preferred active agent according to the present invention is oxybutynin itself. Oxybutynin is a base capable of forming acid addition salts with organic and mineral acids, for example, with hydrochloric acid to form oxybutynin chloride. Preferably, the device of this invention contains oxybutynin as the free base.

As used herein, the term "transdermal" delivery or application refers to the delivery or application of oxybutynin by passage through skin, mucosa and/or other body surfaces by topical application.

As used herein, the term "therapeutically effective" amount or rate refers to the amount or rate of oxybutynin needed to effect the desired therapeutic result.

As used herein, the term "monoesters" refers to those monoesters having from 10 to 20 carbon atoms.

As used herein, the term "glycerol monooleate" refers to glycerol monooleate itself or a mixture of monoglycerides wherein glycerol monooleate is present in the greatest amount.

As used herein, the term "glycerol monolaurate" refers to glycerol monolaurate itself or a mixture of monoglycerides wherein glycerol monolaurate is present in the greatest amount.

As used herein, the term "glycerol monolinoleate" refers to glycerol monolinoleate itself or a mixture of monoglycerides wherein glycerol monolinoleate is present in the greatest amount.

The above summarizes the primary characteristics recognized to date that affect suitability of oxybutynin and a permeation enhancer for transdermal administration. There are undoubtedly others, some of which have not yet been recognized. In order for oxybutynin and a permeation enhancer to be suitable for transdermal administration they must possess the right combination of all of these characteristics, a combination which is quite rare and unpredictable.

SUMMARY OF THE INVENTION

According to the present invention, it has been discovered that oxybutynin may be safely and efficaciously administered transdermally, together with a suitable permeation enhancer, preferably a monoglyceride or mixture of monoglycerides of fatty acids with a total monoester content of at least 51%. The invention includes a transdermal drug delivery device containing sufficient amounts of permeation enhancer and of oxybutynin, in combination, to provide systemic administration of oxybutynin through the skin for a predetermined period of time for the oxybutynin to provide an effective therapeutic result.

The invention is also directed to a method for the transdermal administration of a therapeutically effective amount of oxybutynin together with a skin permeation-enhancing amount of a suitable permeation enhancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-section through a schematic perspective view of one embodiment of transdermal therapeutic devices according to this invention.

FIG. 2 is a cross-section through another embodiment of a transdermal therapeutic device according to this invention.

FIG. 3 is a cross-section through another embodiment of a transdermal therapeutic device according to this invention.

FIG. 4 is a cross-section through yet another embodiment of a transdermal therapeutic device according to this invention.

FIG. 5 shows the oxybutynin permeation rate through the epidermis at 35°C with various permeation enhancers.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

According to the present invention, it has been found that oxybutynin may be administered to the human body in a therapeutically effective amount via the transdermal route when it is co-administered with a suitable permeation enhancer. Therapeutic blood levels from about 0.5 ng/ml to about 3.0 ng/ml can be obtained from administration rates in the range of 0.08 mg/hr to 0.5 mg/hr. Representative skin permeation rates of oxybutynin through living human skin are in the range of about 12 $\mu g/cm^2/hr$ to about 40 $\mu g/cm^2/hr$, depending on the permeation enhancer. Therapeutic blood levels can be achieved within approximately 1-5 hours, and peak blood concentrations are achieved at about 3 hours when the system is worn for 24 hours. The range of desired and achievable system permeation rates of oxybutynin, arriving through the skin from a limited area, is 1-20 mg over a period of 24 hours. The system application is easily adapted for shorter or longer duration treatments, but generally 24 hours is the nominal duration for treatment.

Typical transdermal delivery devices are described in U.S. patent numbers 3,598,122; 3,598,123; 4,286,592; 4,314,557; 4,379,454; 4,559,222; 4,573,995; and 4,849,226, for example. All of these are incorporated herein by reference. The co-administration of

oxybutynin and a permeation enhancer as disclosed herein can be accomplished by using transdermal devices of these kinds.

Because of the wide variation in skin permeability from individual and from site to site on the same body, it may be preferable that oxybutynin and the permeation enhancer be administered from a rate-controlled transdermal delivery device. Rate control can be obtained either through a rate-controlling membrane or adhesive or through the other means disclosed in the patents noted above.

A certain amount of oxybutynin will bind to the skin, and it is accordingly preferred that the skin-contacting layer of the device include this amount of the agent as a loading dose.

Examples of suitable transdermal delivery devices are illustrated in FIGS. 1, 2 and 3. In the drawings, the same reference numbers are used throughout the different figures to designate the same or similar components. The figures are not drawn to scale.

In FIG. 1, transdermal delivery device 10 comprises a reservoir 12 containing both oxybutynin and a suitable permeation enhancer. Reservoir 12 is preferably in the form of a matrix containing oxybutynin and enhancer dispersed therein. Reservoir 12 is sandwiched between a backing layer 14, which is permeable to water vapor, and an in-line contact adhesive layer 16. Preferably, the backing is a spun-laced polyester, such as Sontara®, a nylon reinforced polyurethane, such as NRU-100-C Flexcon® or a multilaminate film layer, such as EVA/EVA/polyvinyldienefluoride /EVA/EVA film layer Saranex® Type 52. The device 10 adheres to the surface of the skin 18 by means of the adhesive layer 16. The adhesive layer 16 may optionally contain enhancer and/or oxybutynin. A strippable release liner (not shown in FIG. 1) is normally provided along the exposed surface of adhesive layer 16 and is removed prior to application of device 10 to the skin 18. Optionally, a rate-controlling membrane (not shown) may be present between the reservoir 12 and the adhesive layer 16.

Alternatively, as shown in FIG. 2, transdermal therapeutic device 20 may be attached to the skin or mucosa of a patient by means

of an adhesive overlay 22. Device 20 is comprised of a oxybutynin- and permeation enhancer-containing reservoir 12 which is preferably in the form of a matrix containing oxybutynin and the enhancer dispersed therein. A backing layer 14, which is impermeable to oxybutynin, the permeation enhancer and water vapor, is provided adjacent one surface of reservoir 12. Adhesive overlay 22 maintains the device on the skin and may be fabricated together with, or provided separately from, the remaining elements of the device. With certain formulations, the adhesive overlay 22 may be preferable to the in-line contact adhesive 16 as shown in FIG. 1. This is true, for example, where the oxybutynin/enhancer reservoir contains a material which adversely affects the adhesive properties of the in-line contact adhesive layer 16. Backing layer 14 is preferably slightly larger than reservoir 12, and in this manner prevents the materials in reservoir 12 from adversely interacting with the adhesive in overlay 22. Optionally, a rate-controlling membrane (not shown in FIG. 2) may be provided on the skin-proximal side of reservoir 12. A strippable release liner 24 is also provided with device 20 and is removed just prior to application of device 20 to the skin.

In FIG. 3, transdermal delivery device 30 comprises a oxybutynin and permeation enhancer containing reservoir ("oxybutynin reservoir") 12 substantially as described with respect to FIG. 1. Permeation enhancer reservoir ("enhancer reservoir") 26 comprises permeation enhancer dispersed throughout and is substantially free of any undissolved oxybutynin. Enhancer reservoir 26 is preferably made from substantially the same matrix as is used to form oxybutynin reservoir 12. A rate-controlling membrane 28 for controlling the release rate of the permeation enhancer from enhancer reservoir 26 to oxybutynin reservoir I2 is placed between the two reservoirs. A rate-controlling membrane (not shown in FIG. 3) for controlling the release rate of the enhancer from oxybutynin reservoir 12 to the skin may also optionally be utilized and would be present between adhesive layer 16 and reservoir I2.

The rate-controlling membrane may be fabricated from permeable, semipermeable or microporous materials which are known in the art to control the rate of agents into and out of delivery devices and having a permeability to the permeation enhancer lower than that of oxybutynin reservoir 12. Suitable materials include, but are not limited to, polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers.

Superimposed over the permeation enhancer reservoir 26 of device 30 is a backing 14 that is permeable to water vapor. On the skin-proximal side of reservoir 12 are an adhesive layer 16 and a strippable liner 24 which would be removed prior to application of the device 30 to the skin.

In the embodiments of FIGS. 1, 2 and 3, the carrier or matrix material of the reservoirs has sufficient viscosity to maintain its shape without oozing or flowing. If, however, the matrix or carrier is a low viscosity flowable material such as a liquid or a gel, the composition can be fully enclosed in a pouch or pocket, as known to the art from U.S. Pat. No. 4,379,454 (noted above), for example, and as illustrated in FIG. 4.

Device 40 shown in FIG. 4 comprises a backing member 14 which serves as a protective cover for the device, imparts structural support, and substantially keeps components in device 40 from escaping the device. Device 40 also includes reservoir 12 which contains the oxybutynin and permeation enhancer and bears on its surface distant from backing member 14 a rate-controlling membrane 28 for controlling the release of oxybutynin and/or permeation enhancer from device 40. The outer edges of backing member 14 overlay the edges of reservoir 12 and are joined along the perimeter with the outer edges of the rate-controlling membrane 28 in a fluid-tight arrangement. This sealed reservoir may be effected by pressure, fusion, adhesion, an adhesive applied to the edges, or other methods known in the art. In this manner, reservoir 12 is contained wholly between backing member 14 and rate-controlling membrane 28. On the skin-proximal side of rate-controlling membrane 28 are an adhesive

layer 16 and a strippable liner 24 which would be removed prior to application of the device 40 to the skin.

In an alternative embodiment of device 40 of FIG. 4, reservoir 12 contains the permeation enhancer only and is substantially free of oxybutynin. The oxybutynin and an additional amount of permeation enhancer are present in adhesive layer 16 which acts as a separate reservoir.

The oxybutynin and the permeation enhancer can be co-extensively administered to human skin or mucosa by direct application to the skin or mucosa in the form of an ointment, gel, cream or lotion. for example, but are preferably administered from a skin patch or other known transdermal delivery device which contains a saturated or unsaturated formulation of oxybutynin and the enhancer.

The formulation may be aqueous or non-aqueous based. The formulation should be designed to deliver the oxybutynin and the permeation enhancer at the necessary release rates. Aqueous formulations typically comprise water or water/ethanol and about 1-2 wt % of a gelling agent, an example being a hydrophilic polymer such as hydroxyethylcellulose or hydroxypropylcellulose. Typical non-aqueous gels are comprised of silicone fluid or mineral oil. Mineral oil-based gels also typically contain 1-2 wt % of a gelling agent such as colloidal silicon dioxide. The suitability of a particular gel depends upon the compatibility of its constituents with both the oxybutynin and the permeation enhancer and any other components in the formulation.

The reservoir matrix should be compatible with oxybutynin, the permeation enhancer and any carrier therefor. The term "matrix" as used herein refers to a well-mixed composite of ingredients fixed into shape. When using an aqueous-based formulation, the reservoir matrix is preferably a hydrophilic polymer, e.g., a hydrogel. When using a non-aqueous-based formulation, the reservoir matrix is preferably composed of a hydrophobic polymer. Suitable polymeric matrices are well known in the transdermal drug delivery art, and

examples are listed in the above-named patents previously incorporated herein by reference.

A typical laminated system would comprise a polymeric membrane and/or matrix such as ethylene vinyl acetate (EVA) copolymers, such as those described in U.S. Pat. No. 4,144,317, preferably having a vinyl acetate (VA) content in the range of from about 9% up to about 60% and more preferably about 28% to about 60% VA. Polyisobutylene/oil polymers containing from 4-25% high molecular weight polyisobutylene and 20-81% low molecular weight polyisobutylene with the balance being an oil such as mineral oil or polybutynes may also be used as the matrix material.

The aforementioned patents describe a wide variety of materials which can be used for fabricating the various layers or components of the transdermal oxybutynin delivery devices according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

The amount of oxybutynin present in the therapeutic device and required to achieve an effective therapeutic result depends on many factors, such as the minimum necessary dosage of oxybutynin for the particular indication being treated; the solubility and permeability of the matrix, of the adhesive layer and of the rate-controlling membrane, if present; and the period of time for which the device will be fixed to the skin. The minimum amount of oxybutynin is determined by the requirement that sufficient quantities of oxybutynin must be present in the device to maintain the desired rate of release over the given period of application. The maximum amount for safety purposes is determined by the requirement that the quantity of oxybutynin present cannot exceed a rate of release that reaches toxic levels. The oral lethal dose discovered for rats is 1220 mg/kg.

When a constant oxybutynin delivery rate is desired, the oxybutynin is normally present in the matrix or carrier at a concentration in excess of saturation, the amount of excess being a

function of the desired length of the oxybutynin delivery period of the system. The oxybutynin may, however, be present at a level below saturation without departing from this invention as long as oxybutynin is continuously administered to the same skin or mucosa site in an amount and for a period of time sufficient to provide the desired therapeutic rate and delivery profile of oxybutynin delivery.

The permeation enhancer is dispersed through the matrix or carrier, preferably at a concentration sufficient to provide permeation-enhancing amounts of enhancer in the reservoir throughout the anticipated administration period. Where there is an additional, separate permeation enhancer matrix layer as well, as in FIGS. 3 and 4, the permeation enhancer normally is present in the separate reservoir in excess of saturation.

The preferred permeation enhancers of the present invention are a monoglyceride or a mixture of monoglycerides of fatty acids with a total monoester content of at least 51%. Fatty acids may be saturated or unsaturated and straight or chained, and include, for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid and palmitic acid. Monoglycerides are generally available as a mixture of monoglycerides, with the mixture deriving its name from the monoglyceride present in the greatest amount. Monoglyceride permeation enhancers include, for example, glycerol monooleate, glycerol monolaurate and glycerol monolinoleate. In a more preferred embodiment, the permeation enhancer is glycerol monooleate.

In addition to oxybutynin and a suitable permeation enhancer, which are essential to the invention, the matrix or carrier may also contain dyes, pigments, inert fillers, excipients and other conventional components of pharmaceutical products or transdermal devices known to the art.

In the present invention, oxybutynin is delivered at a therapeutically effective rate (that is, a rate that provides a desired therapeutic effect) and the permeation enhancer is delivered at a permeation-enhancing rate (that is, a rate that provides

increased permeability of the application site to the oxybutynin) for a predetermined time period and in the required delivery pattern.

A preferred embodiment of the present invention comprises a method of treating any disorder in which it is therapeutic to administer a therapeutically effective amount of one or more of the compounds of the present invention to a patient suffering from such disorder.

Another preferred embodiment of the present invention comprises a method of treating neurogenic bladder disorders, e.g., urinary frequency or incontinence. To be useful in treating a neurogenic bladder disorder. oxybutynin should be present in plasma at levels above about 0.5 ng/ml, preferably at levels above about 1.0 ng/ml and most preferably at levels of about 2.0 ng/ml. To achieve this result, oxybutynin is delivered at a therapeutic rate of at least about 40-200 μg per hour, but typically of at least 80 μg/hr, and more typically at about 80-160 μg/hr, for the treatment period, usually about 24 hours to 7 days.

The administration rate through the skin should be sufficient to minimize the size of the device. The size of the device of this invention can vary from less than 1 cm^2 to greater than 200 cm^2. A typical device, however, will have a size within the range of 5-50 cm^2. The delivery device containing the oxybutynin and a permeation enhancer is placed on a user such that the device is delivering oxybutynin in a therapeutically effective amount to the user to treat a neurogenic bladder disorder.

The length of time of oxybutynin presence and the total amount of oxybutynin in the plasma can be changed following the teachings of this invention to provide different treatment regimens. Thus, they can be controlled by the amount of time during which exogenous oxybutynin is delivered transdermally to an individual or animal.

The devices of this invention can be designed to effectively deliver oxybutynin for an extended time period of from several hours up to 7 days or longer. Seven days is generally the maximum time limit for application of a single device because the adverse affect of occlusion of a skin site increases with time and the normal cycle

of sloughing and replacement of the skin cells occurs in about 7 days. The transdermal therapeutic devices of the present invention are prepared in a manner known in the art, such as by those procedures, for example, described in the transdermal device patents listed previously herein. Having thus generally described the invention, the following specific examples describe preferred embodiments thereof.

DETAILED DESCRIPTION OF EXAMPLES

The devices for Example 1 were prepared as follows:

A. Formulation without a Permeation Enhancer

A formulation containing 30 wt % oxybutynin base in a matrix of EVA 40 (U.S.I. Chemicals, Illinois) was prepared by dissolving the oxybutynin base and EVA 40 in methylene chloride. The solution was poured onto a sheet of fluorocarbon diacrylate ("FCD")/polyester release liner to dry. The dried material was pressed to 5 mil (a. 0.1 mm) thickness between two sheets of FCD/polyester release liner at 75°C. The resulting film was laminated to a flexible cloth backing (spun laced polyester, 1.3 oz/yd^2), and 2.0 cm^2 discs were cut from the laminate.

B. Formulations with Permeation Enhancers

Formulations containing oxybutynin base at 30 wt %, and various permeation enhancers glycerol monolaurate, glycerol monooleate, and glycerol monolinoleate) at 25 wt % in a matrix of EVA 40 were prepared by dissolving the oxybutynin base, permeation enhancer and EVA 40 in methylene chloride. The same procedure as described above was then used to make the device.

The glycerol monooleate (GMO) used was Myverol® 18-99K glycerol monooleate (Eastman Kodak Chemicals), which has a glycerol monooleate content of 61% and a total monoester content of 93%, the glycerol monolinoleate (GMLO) used was Myverol® 18-92K glycerol monolinoleate, which has a glycerol monolinoleate content of 68% and a minimum total monoester content of 90%, and the glycerol monolaurate (GML) used was Grindtek® ML 90 glycerol monolaurate, which has a glycerol

monolaurate content of 90% and a minimum total monoester content of 90%.

C. Device with In-line Adhesive

Each of the oxybutynin matrix/cloth backing laminates were divided in half, and one half of each was laminated to 3M acylate transfer adhesive MSP 32589 (1.6 mil, an acrylate adhesive with 2-5% acid functionality). Before testing, each final laminate was equilibrated for at least 5 days to allow the enhancer and oxybutynin to partition into the contact adhesive. The edges of the devices with in-line adhesive were masked with polyester tape so that the oxybutynin reservoir edges were not exposed to the epidermis or solutions when they were tested.

The devices for Examples 2, 4 and 5 are prepared as follows:

A. Formulation containing GMO

A formulation containing 27 wt % oxybutynin base and 27 wt % GMO (Myverol® 18-99K glycerol monooleate) in a matrix of EVA 40 was prepared using a Brabender Mixer and a 50 cc mixing bowl. The EVA 40 was added to the mixing bowl and mixed until pellets were no longer visible. The oxybutynin base was slowly added to the mixing bowl. Mixing was continued for an additional 10 minutes after addition was complete. GMO was heated to 40°C and added very slowly to the mixing bowl. Addition time was approximately 45 minutes. The bowl was then closed and mixing continued for at least 20 minutes before removing the completed oxybutynin mix from the bowl.

The oxybutynin mix was calendared to 5 mil thickness between release liners (FCD/polyester). Five one-foot sections of the oxybutynin film were heat laminated to Medpar® backing (medium density polyethylene layer/aluminum polyester layer/EVA layer). Three of the oxybutynin film/backing laminates were laminated to 3M acrylate transfer adhesive MSP 1006 P.

EXAMPLE 1

The in vitro transdermal oxybutynin permeation rates through the epidermis of two human skin donors from devices described above were determined. For each device tested, the release liner was removed and the oxybutynin-releasing surface was placed against the stratum corneum side of a disc of human epidermis which had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon® holder of a release rate rod using nylon mesh and metal string. The rods were reciprocated in a fixed volume of receptor solution 0.05 M phosphate buffer, pH 6.5. The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

Results are summarized in the following table:

TABLE 1

	Permeation Enhancer	Average Transdermal Oxybutynin (Base) Permeation Rate $\mu g/cm^2/hr$ for 0-96 hrs
With adhesive	None (control)	1.21
	GML	3.74
	Myverol® 18-99K	3.09
	Myverol® 18-92K	2.40
Without adhesive	None Control	1.13
	GML	4.24
	Myverol® 18-99K	3.59
	Myverol® 18-92K	2.47

EXAMPLE 2

The in vitro transdermal oxybutynin permeation rates through the epidermis of five human skin donors from devices described above were determined as described in Example 1. The control formulation contained 30 wt % oxybutynin base (no permeation enhancer) in an EVA 40 matrix. No in-line adhesive was present. The other formulation

contained 28 wt % oxybutynin base and 28 wt % Myverol® 18-99K glycerol monooleate in an EVA 40 matrix. There was a 3M acrylate in-line adhesive present. This same device was used in the in vivo testing described in Examples 3 and 4. The results are summarized in the following table:

TABLE 2

Skin Donor	Control Without Permeation Enhancer $\mu g/cm^2/hr$	With Permeation Enhancer $\mu g/cm^2/hr$
1	4.7	15.4
2	3.1	6.8
3	2.6	9.4
4	2.5	4.7
5	2.6	5.4

EXAMPLE 3

This experiment was carried out using standard glass diffusion cells which consist of a donor compartment with a 4 ml capacity, and a receptor compartment with a 22 ml capacity. A circular piece of epidermis was placed in each diffusion cell (permeation area = 1.13 cm^2) in a horizontal position between a lower capped receptor compartment and an upper capped donor compartment. The receptor compartment has both a venting tube (uncapped) and a sampling port (capped). The stratum corneum side of the epidermis faced the donor compartment. An O-ring was positioned between the epidermis and the donor compartment, and a clamp held the compartments together. The receptor solution, 22 ml of 0.05 M phosphate buffer solution, pH 6.5, was added to each receptor compartment. The cells were placed in a temperature controlled water bath shaker at 35°C and allowed to come to temperature before the donor solution was added.

A total of five donor solutions were tested, and the donor volume was 0.2 ml in each case. The donor solutions tested were oxybutynin saturated in 0.05 M phosphate buffer solution, pH 6.5, oxybutynin saturated in mineral oil, oxybutynin saturated in a solution of 30% ethanol in phosphate buffer, oxybutynin saturated in a solution of 10.6% Myverol 18-99K glycerol monooleate in mineral

oil, and oxybutynin saturated in a solution of 10.6% glycerol monolaurate in mineral oil. All donor solutions were at pH 6.5.

At each time interval, the receptor solution was removed from the test cell and replaced with an equal volume of fresh receptor solution previously equilibrated at 35°C. The receptor solutions for each time interval were then assayed for oxybutynin, by HPLC (Zorbax Rx-C8, 15 cm x 4.6 mm ID, 5 μm, 30% acetonitrile/water, 0.06% dimethyloctylamine, 0.03% H_3PO_4, 220 nm, 1.0 ml/min), to calculate the permeation rate of oxybutynin through epidermis from the donor solution.

As can be seen in Figure 5, glycerol monolaurate and glycerol monolinoleate increased the permeation rate of oxybutynin, whereas ethanol showed the same permeation rate as the donor solution containing no permeation enhancer.

EXAMPLE 4

The in vivo plasma levels of oxybutynin were measured for two body sites. A 10 cm^2 device was worn on the penis for 10½ hours and two 10 cm^2 devices were worn on the inner thigh for 24 hours. A control sample was drawn before applying the systems. The device worn on the penis produced a plasma oxybutynin level of 2.0 ng/mL within 4 hours, and the levels varied between 1.4 and 2.1 ng/mL during the following 6½ hours of wearing. The systems worn on the inner thigh produced a plasma oxybutynin concentration of 0.9 ng/mL after 12 hours of wearing, and after 24 hours of wearing the level had reached 1.1 ng/mL.

The in vivo plasma oxybutynin concentration were also measured in two additional subjects who each wore two 10 cm^2 systems on the inner thigh. One subject achieved a plasma oxybutynin concentration of 2.0 ng/mL after 9 hours, and the plasma level was 1.7 ng/mL after 24 hours of wearing. The other subject achieved a plasma level of 0.7 ng/mL after 12 hours, and the plasma level was 0.8 ng/mL after 24 hours.

EXAMPLE 5

The residual oxybutynin in devices which had been worn by subjects was measured and compared to the oxybutynin content of devices which had not been worn. The results are summarized in the following table:

TABLE 3

Subject #	Site	Measured Drug Loss (mg/20 cm^2/day)
1	inner thigh	5.8
2	inner thigh	8.6
3	chest	6.7
4	abdomen	7.2
5	penis	19.2

Having thus generally described the present invention and described certain specific embodiments thereof including the embodiments that the applicants consider the best mode of practicing their invention, it will be readily apparent that various modifications to the invention may be made by workers skilled in the art without departing from the scope of this invention which is limited only by the following claims.

WHAT IS CLAIMED IS:

1. A device for the transdermal administration, at a therapeutically effective rate, of oxybutynin, which device comprises:

(a) a reservoir comprising a therapeutically effective amount of oxybutynin and a skin permeation-enhancing amount of a permeation enhancer;

(b) a backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in oxybutynin- and permeation enhancer-transmitting relation with the skin.

2. A device according to Claim 1 wherein the permeation enhancer is a monoglyceride or a mixture of monoglycerides of a fatty acids with a total monoesters content of at least 51%.

3. A device according to Claim 2 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

4. A device according to Claim 1 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

5. A device according to Claim 1 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

6. A device according to Claim 1 wherein the backing is permeable to water vapor.

7. A device according to Claim 1 wherein the permeation enhancer is glycerol monooleate and the reservoir further comprises a

matrix containing ethylene vinyl acetate copolymer having from about 9% to 60% vinyl acetate.

8. A device according to Claim 6 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir.

9. A device for the transdermal administration, at a therapeutically effective rate, of oxybutynin, which device comprises:

(a) a first reservoir comprising a therapeutically effective amount of oxybutynin and a skin permeation-enhancing amount of a permeation enhancer;

(b) a second reservoir comprising an excess of the permeation enhancer and substantially free of oxybutynin;

(c) a rate-controlling membrane between the first reservoir and the second reservoir;

(d) a backing on the skin-distal surface of the second reservoir; and

(e) means for maintaining the first and second reservoirs in oxybutynin- and permeation enhancer-transmitting relation with the skin.

10. A device according to Claim 9 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

11. A device according to Claim 9 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

12. A device according to Claim 9 wherein the backing is permeable to water vapor.

13. A device according to Claim 9 wherein the means for maintaining the reservoirs in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the first reservoir.

14. A device according to Claim 9 wherein the first reservoir also is an adhesive layer which functions as the means for maintaining the reservoirs in relation with the skin.

15. A device according to Claim 9 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

16. A device according to Claim 15 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

17. A method for the transdermal administration of oxybutynin, which method comprises:

(a) administering oxybutynin at a therapeutically effective rate to an area of skin; and

(b) simultaneously administering a permeation enhancer to the area of skin at a rate which is sufficient to substantially increase the permeability of the area to the oxybutynin.

18. A method according to Claim 17 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

19. A method according to Claim 18 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

20. A method according to Claim 17 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

21. A method according to Claim 17 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

22. A method according to Claim 17 wherein the backing is permeable to water vapor.

23. A method for treating neurogenic bladder disorders, the method comprising the step of placing a oxybutynin transdermal delivery device onto the skin of a person, the oxybutynin transdermal delivery device comprising:

(a) a reservoir comprising oxybutynin in an amount sufficient to provide treatment of symptoms of a neurogenic bladder for a predetermined period of time and a permeation enhancer in a skin permeation-enhancing amount;

(b) a backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in oxybutynin- and permeation enhancer-transmitting relation with the skin.

24. A method according to Claim 23 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

25. A method according to Claim 24 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

26. A method according to Claim 23 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for the predetermined period of time.

27. A method according to Claim 23 wherein the oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

28. A method according to Claim 23 wherein the backing is permeable to water vapor.

29. A method according to Claim 23 wherein the permeation enhancer is glycerol monooleate and the reservoir further comprises a matrix comprising ethylene vinyl acetate copolymer having from about 9% to 60% vinyl acetate.

30. A method according to Claim 29 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir.

31. A method for treating neurogenic bladder disorders, the method comprising the step of placing a oxybutynin transdermal delivery device onto the skin of a person, the oxybutynin transdermal delivery device comprising:

(a) a first reservoir comprising oxybutynin in an amount sufficient to provide treatment of symptoms of a neurogenic bladder for a predetermined period of time and a permeation enhancer in a skin permeation-enhancing amount;

(b) a second reservoir comprising an excess of the permeation enhancer and substantially free of oxybutynin;

(c) a rate-controlling membrane between the first reservoir and the second reservoir;

(d) a backing on the skin-distal surface of the second reservoir; and

(c) means for maintaining the first and second reservoirs in oxybutynin- and permeation enhancer-transmitting relation with the skin.

32. A method according to Claim 31 wherein the oxybutynin is administered through the skin at a rate of at least 0.08 mg/hour for a predetermined period of time.

33. A method according to Claim 31 wherein oxybutynin is administered through the skin at a permeation rate of at least 12 $\mu g/cm^2/hr$ for a predetermined period of time.

34. A method according to Claim 31 wherein the backing is permeable to water vapor.

35. A method according to Claim 31 wherein the means for maintaining the reservoirs in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the first reservoir.

36. A method according to Claim 31 wherein the first reservoir also is an adhesive layer which functions as the means for maintaining the reservoirs in relation with the skin.

37. A method according to Claim 31 wherein the permeation enhancer is a monoglyceride or mixture of monoglycerides of fatty acids with a total monoesters content of at least 51%.

38. A device according to Claim 37 wherein the permeation enhancer is glycerol monooleate, glycerol monolaurate or glycerol monolinoleate.

FIG. 1

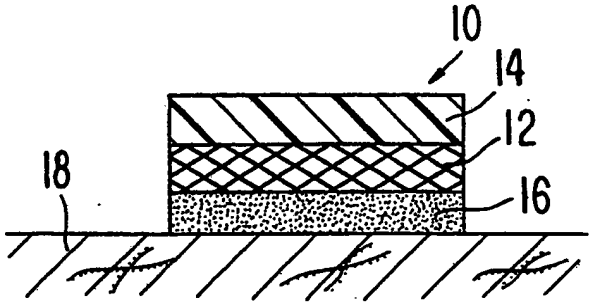


FIG. 2

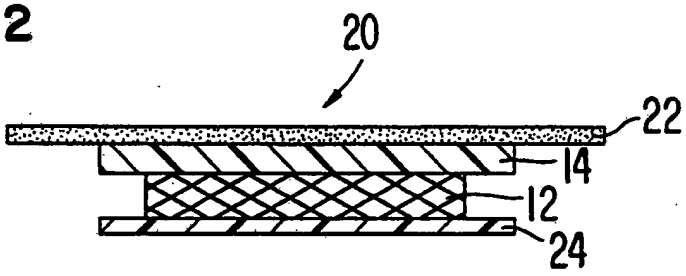


FIG. 3

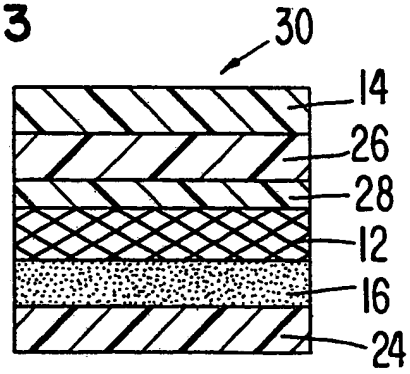


FIG. 4

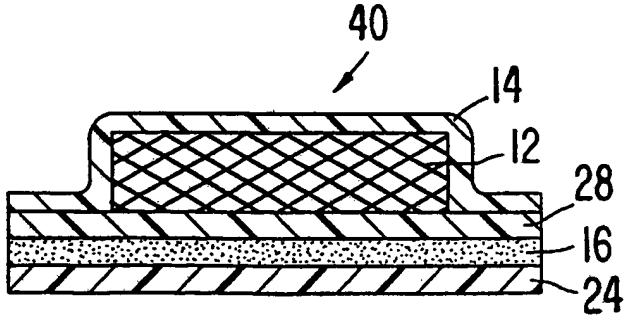
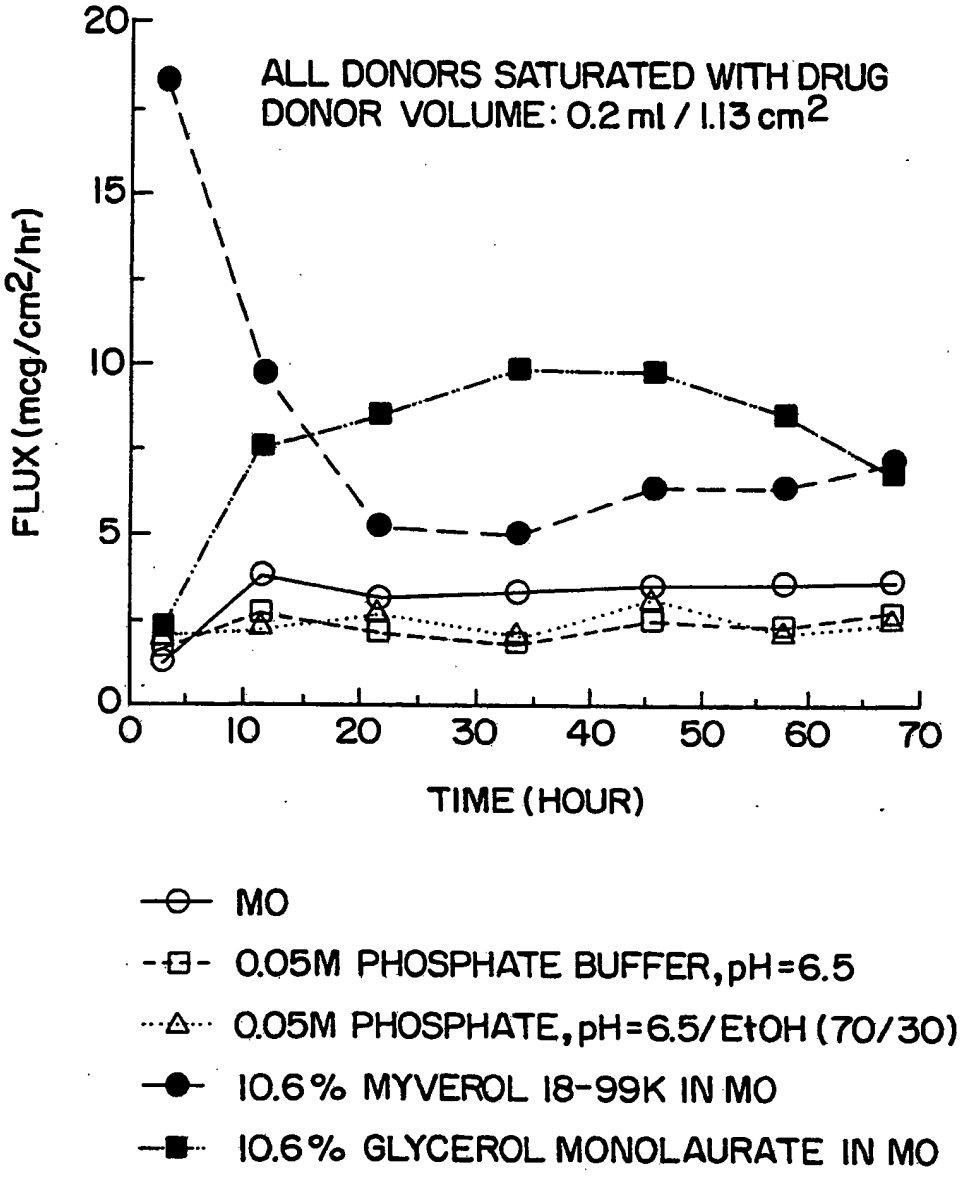


FIG. 5


ALL DONORS SATURATED WITH DRUG
DONOR VOLUME: 0.2 ml / 1.13 cm2
FLUX (mcg/cm2/hr)
TIME (HOUR)
0
5
10
15
20
0
10
20
30
40
50
60
70
MO
0.05M PHOSPHATE BUFFER, pH=6.5
0.05M PHOSPHATE, pH=6.5/EtOH (70/30)
10.6% MYVEROL 18-99K IN MO
10.6% GLYCEROL MONOLAURATE IN MO

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04518

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/135; A61K9/70; A61K47/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 250 125 (SMITH & NEPHEW) 23 December 1987 cited in the application see claims	1-38
A	US,A,4 747 845 (B.KOROL) 31 May 1988 cited in the application see claims see column 9, line 46	1-38
A	DATABASE WPIL Week 9219, Derwent Publications Ltd., London, GB; AN 92-157308 (19) & JP,A,04 099 719 (RIDO CHEMICAL KK) 31 March 1992 see abstract	1-38

-/--

[10] Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 AUGUST 1993	31. 08. 93 31.08.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	WO,A,9 220 377 (ALZA CORPORATION) 26 November 1992 see claims see example 5	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/04518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 17-37 are directed to a method of treatment of the human body by therapy (Rule 39.1(IV)PCT), the search has been carried out and based upon the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304518
SA 74136

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0250125	23-12-87	AU-B- 609398	02-05-91
		AU-A- 7378987	10-12-87
		CA-A- 1272922	21-08-90
		GB-A- 2191943	31-12-87
		JP-A- 63029661	08-02-88
		US-A- 4784857	15-11-88
US-A-4747845	31-05-88	US-A- 4563184	07-01-86
		US-A- 4857334	15-08-89
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		AU-B- 563517	09-07-87
		AU-A- 3362384	26-04-85
		CA-A- 1245158	22-11-88
		EP-A,B 0138740	24-04-85
		EP-A- 0344090	29-11-89
		JP-A- 60150755	08-08-85
		US-A- 4725271	16-02-88
WO-A-9220377	26-11-92	AU-A- 2010392	30-12-92

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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		(43) International Publication Date: 2 May 1996 (02.05.96)

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(74) Agent: OY JALO ANT-WUORINEN AB; Iso Roobertinkatu 4-6 A, FIN-00120 Helsinki (FI).

(81) Designated States: AM, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LT, LV, NO, NZ, PL, RO, RU, SI, SK, TJ, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: CONTROLLED RELEASE ORAL DELIVERY SYSTEM CONTAINING OXYBUTYNIN

(57) Abstract

The present invention concerns a controlled release drug delivery system for oxybutynin, its manufacture and use. The drug delivery system comprises oxybutynin in combination with a controlled release excipient comprising about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of 1:3 to 3:1, a cationic crosslinking agent for the said hydrophilic material, in an amount of 1 to 20 % by weight, and 20-79 % by weight of an inert filler.

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Controlled release oral delivery system containing oxybutynin.

The present invention relates to controlled or extended release delivery systems for the treatment of disorders responsive to the action of an antispasmodically active agents, especially for the treatment of a neurogenic bladder, a method of preparation of the delivery systems as well as method of using them.

Oxybutynin and its salts, in particular the hydrochloride (hereinafter oxybutynin) is a musculotropic antispasmodic drug with moderate anticholinergic, systemic analgesic and local anaesthetic action. Its relaxant effect on smooth muscle is based on antagonism of a process distal to the neuromuscular junction (papaverine-like effect) and on anticholinergic action on the blockage of muscarine-type receptors. Oxybutynin chloride has been in clinical use for twenty years and it is indicated for the relief of symptoms associated with voiding in patients with an uninhibited neurogenic and reflex neurogenic bladder. It is also used to suppress gastric acid secretion, to relieve post-transurethral vesical pain and spasm in the gastrointestinal tract, to control detrusor dysfunction and to facilitate catheterization of the urinary bladder in myelomeningocele patients. The drug is effective when given orally.

Chemically, oxybutynin hydrochloride (DL-racemic form of 4-diethylamino-2-butynyl-phenyl-cyclohexylglycolate hydrochloride) is a tertiary amine. It is rapidly absorbed from the gastrointestinal tract following oral administration and its pharmacological action starts within one hour. The duration of action of the drug is three to six hours.

It has been established that after the administration of oxybutynin hydrochloride (5 mg dose tablet), the maximum concentration of unmetabolized oxybutynin in plasma was

reached within 1 h, and the elimination half-life was about 2.5 h. Due to the relatively rapid elimination of the active agent from the blood, conventional treatment with oxybutynin has comprised administering oxybutynin in a dose of 5 mg (calculated as the hydrochloride) twice or three times daily, the recommended maximal dose of oxybutynin being 20 mg per day.

In conventional treatment, the administration of oxybutynin is accompanied by a high initial peak concentration in the blood with associated side effects. Furthermore, the frequent need to administer the drug in order to maintain or restore the necessary concentration of active agent in the blood is cumbersome and consequently has a tendency to reduce patient compliance.

Consequently, there is a need for an oxybutynin preparation with a sustained action. Especially there is a need for a preparation which allows for a reduction of the peak initial drug concentration in the blood and which provides for an even and substantially extended effect. Such a preparation would readily allow for a once-a-day treatment with a single oral dose.

According to the invention the afore mentioned aim has been reached by combining oxybutynin or a pharmaceutically acceptable salt thereof, with an excipient allowing the controlled and extended, even release of the active agent over a period of time exceeding 24 hours while simultaneously reducing the initial peak concentrations of active agent in the blood of the patient.

Thus the invention provides a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin,

or a pharmaceutically acceptable salt thereof,

- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

The excipient used in the composition according to the invention thus comprises as one component a hydrophilic material or gelling system comprising on the hand a heteropolysaccharide, and on the other hand a homopolysaccharide which is capable of crosslinking the heteropolysaccharide in an aqueous fluid, such as in a gastric fluid, the ratio between the two types of saccharides being from about 3:1 to 1:3.

The heteropolysaccharide is a water soluble saccharide containing two or more kinds of sugar units, and it has excellent swelling properties. According to a preferred embodiment it comprises a xanthan gum, or a derivative thereof. Such derivatives are deacylated xanthan gum, the carboxymethyl ether and propylene glycol ester.

In the preferred embodiment, the homopolysaccharide comprises one or more galactomannans, and especially galactomannas with a higher ratio of mannose to galactose, e.g. locust bean gum. Other polysaccharides are e.g. guar gum and hydroxypropyl guar gum.

The ratio between heteropolysaccharide and homopolysaccharide is preferably approximately 1:1.

In addition the excipient contains an inert filler or diluent, which suitably is a monosaccharide, disaccharide or polyhydric alcohol, such as sucrose, dextrose, lactose, fructose, xylitol, sorbitol, and microcrystalline cellulose, or mixtures thereof.

The excipient used in the composition according to the invention contains in addition a cationic crosslinking agent which is capable of crosslinking the hydrophilic material, when this is exposed to gastrointestinal fluids, thus strengthening the gel structure and preventing an initial burst of the drug when exposed to a gastrointestinal environment. The amount of cationic crosslinking is at the most about 20 % by weight, such as from bout 1 to 20, especially about 5 to 15 % by weight.

The cationic crosslinking agent can be a mono- or multivalent salt, preferably an inorganic salt such as alkali and/or alkaline earth metal salt, such as sodium, potassium, litium, calcium, magnesium chloride, bromide, sulfate, borate, citrate, acetate, lactate, carbonate, bicarbonate. The cationic crosslinking agent is preferably divalent, such as in calcium sulfate, or it is sodium chloride.

Controlled release excipients containing a combination of hetero- and homopolysaccharides as defined above with inert diluents, have been described in the US patents 4,994,276, 5,128,143, and 4,135,757.

In a preferred embodiment the excipient contains about 25 to 50, especially about 25 to 35 % by weight of the hydrophilic material or gelling system, about 5 to 15 % by weight of cationic crosslinking agents, and about 35 to 70, especially about 50 to 70 % by weight of inert diluent.

The ratio of oxybutynin (calculated as its hydrochloride) to hydrophilic material is preferably about 1:5 to 1:15. A suitable amount of oxybutynin in a single dose, such as in a tablet, is about 5 to 20 mg, especially about 10 mg. A suitable daily dose of opxybutynin is from about 0.05 to 0.25 mg/kg body weight, especially appr. 0.12 mg/kg body weight.

The drug delivery system according to the invention can be made by first dry blending the ingredients for the excipient, and then granulating the mixture in the presence of small amount of fluid, such as water. The obtained granulate is therafter combined with the active ingredient for example by simple dry-blending, or by using wet granulation techniques, using e.g. water as the granulating fluid.

According to an embodiment of the invention, a suitable lubricant, known per se, can be added to the excipient and drug components to be combined. The choice of lubricants is well known in the art, and magnesium, calcium and sodium stearate may be mentioned. A suitable amount of lubricant is appr. 0,5 to 3 % by weight.

The drug-excipient mixture prepared may be compressed to tablets according to conventional tablet formation techniques. The blend may also be used as pellets, as a granulate or powder, or filled in capsules. The dosage formed obtained may be coated using any suitable coating system. Such coating systems and coating techniques are well known in the art.

According to the invention it is possible to add to the composition further agents and additives, e.g. hydrophobic agents for regulating the hydration of the product, for example by including polymeric cellulose derivatives, such as alkyl celluloses, polymeric acrylic and methacry-

lic acid derivatives, waxes, oils etc. usually in amounts amounting to about 1 to 20 % by weight. Such an addition replaces part of the inert diluent. The hydrophobic agents are as such well known in the art, and a number of them are commercially available. It is also possible to add release rate decreasing substances to the mixture of drug and excipient, for example microcrystalline cellulose in an amount of about 1 to 10 % by weight.

The present invention also concerns a method for treating a subject of a condition responsive to the action of an antispasmodically active agent, such as voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction, especially of neurogenic bladder, the method comprising administering to the subject for oral ingestion a delivery system, especially a tablet, according to the invention as defined above.

The invention also concerns a method of maintaining, in a human subject, a therapeutically sufficient blood level concentration of oxybutynin or of an active metabolite thereof, such as N-desethyl oxybutynin, for an extended period of time, the method comprising administering orally to the said subject a controlled release delivery system according to the invention, as defined above, especially a tablet containing 5 to 20 mg of oxybutynin. Preferably a therapeutically sufficient blood level concentration is maintained for at least about 24 hours after administration of a single dose of oxybutynin, such as a single dose of about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight, of oxybutynin or a salt thereof, e.g. the hydrochloride. The administration of a daily single dose of a 10 mg controlled release oxybutynin tablet gave blood level concentrations of oxybutynin of at least about 0.5 ng/ml, such as 0.5 to 2.0 ng/ml for a period of at least about 24 hours, the value following

the peak value being in the area of about 0.5 to 1.0 ng/ml, as is evident from the test report.

The following examples illustrate the invention, however, without limiting the scope thereof. Parts and percentages are by weight, unless otherwise stated.

Examples 1 - 2:

In Examples 1-2, controlled release excipients in accordance with the present invention were first prepared, the oxybutynin being added subsequently, and the final mixture then being tableted.

The excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, calcium sulfate, and dextrose in a high speed mixer/granulater for 2 minutes. While running choppers/impellers, the requisite amount of water was added to the dry blended mixture, and granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a LOD (loss on drying) of less than about 10% by weight (e.g. 4-7% LOD). The granulation was then milled using 20 mesh screens. The ingredients of the granulations of Examples 1-2 are set forth in Table 1 below:

TABLE 1

Preparation of sustained-release excipient

Component	% - Ex. 1	% - Ex. 2
1. Xanthan Gum	25	25
2. Locust Bean Gum	25	25
3. Dextrose	40	30
4. Calcium Sulfate	10	20
5. Water	10*	10*

*Removed during processing.

Next, the excipient prepared as detailed above was dry blended with the desired amount of oxybutynin HCl in a V-blender for 10 minutes. A suitable tableting lubricant (Pruv®, sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc) was added, and the mixture was blended for another 5 minutes. This final mixture was compressed into tablets. The ingredients of the tablets of Examples 1-2 are set forth in Table 2 below:

TABLE 2

Tablet formulation - Examples 1-2

Component	% - Ex. 1	% - Ex. 2
1. Excipient	93.8	93.8
2. Oxybutynin HCl	4.7	4.7
3. Sodium stearyl fumarate	1.5	1.5
Tablet weight (mg)	213.2	213.2
Hardness (Kp)	3.3	1.4

Examples 3-4:

In Examples 3-4, a controlled release excipient was prepared in accordance with the procedures set forth for Examples 1-2. The ingredients of the sustained release matrix of Examples 3-4 are set forth in Table 3 below:

TABLE 3

Component	% - Ex. 3	% - Ex. 4
1. Xanthan Gum	15	15
2. Locust bean Gum	15	15
3. Dextrose	60	60
4. Calcium Sulfate	10	10
5. Water	10*	10*

*Revomed during prosessing.

Thereafter, oxybutynin tablets were prepared in accordance with the procedure set forth in Examples 1-2. The ingredients of the tablets of Examples 3-4 are set forth in Table 4 below:

TABLE 4

Component	% - Ex. 3	% - Ex. 4
1. Excipient	95.7	93.0
2. Oxybutynin HCl	2.9	5.6
3. Sodium stearyl fumarate	1.4	1.4
Tablet weight (mg)	348.3	179.3
Hardness (Kp)	10.4	3.3

In Example 3, the drug:gel ratio is about 1:10. In Example 4, the drug:gel ratio is about 1:5. By "gel" it is meant the combined weight of xanthan gum and locust bean gum.

TEST REPORT

A bioequivalence study was carried out to assess the bioavailability of oxybutynin from a delivery system according to the invention, using as a reference system an ordinary 5 mg oxybutynin chloride containing tablet, after a single peroral dose of 10 mg of oxybutynin chloride.

The study was performed as a balanced, randomized, three-period cross-over study on 24 healthy volunteers.

Pharmacokinetics

From serum concentrations of oxybutynin and its metabolite N-desethyl oxybutynin the following pharmacokinetic parameters were calculated:

- AUC_{0-t} using the linear trapezoidal rule (t was the last detectable concentration).
- C_{max} and t_{max} were used as measured

The individual and mean serum time-concentration curves for both oxybutynin and its metabolite N-desethyl oxybutynin were provided.

The pharmacokinetic parameters were calculated and curves created using the Siphar program.

Fourteen (14) blood samples (10 ml each) were taken during each study period according to the following schedule: 0 (pre-drug), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours following drug administration. A total of 420 ml blood was taken over the three study phases, exclusive of pre- and post-clinical blood work (30 ml).

All urine excreted during 24 h after administration of the drug was collected as follows: one sample was taken before administration (blank sample); thereafter, samples in fractions of four hours up to 12.0 h after administration (0.0-4.0 h, 4.0-8.0 h and 8.0-12.0 h), and in a fraction of twelve hours up to 24.0 h (12.0-24.0 h).

Urine fractions were measured by volume, and aliquots of 2-3 ml separated into duplicate polypropylene tubes, frozen immediately and stored at -20°C for later examination.

Evaluations

The data from this study was analyzed by comparing the pharmacokinetic parameters calculated for the controlled release tablet (test preparation) to those for the ordinary tablet (reference preparation).

Analytical methods

Analysis of oxybutynin and its metabolite N-desethyl oxybutynin in serum were carried out by a capillary gas chromatographic method using mass selective detector. The quantification limit of the method was 0.2 ng/ml for unchanged oxybutynin and 2.5 ng/ml for the metabolite. The method is linear from 0.2 ng/ml to 30 ng/ml for oxybutynin and from 2.5 to 150 ng/ml for N-desethyl oxybutynin, respectively.

Results

There were no statistically significant differences in the extent of oxybutynin in serum after administration of the controlled release tablet (Md AUC_{0-t}= 17.02 ng/ml*h) compared to that after intake of two 5 mg ordinary tablets (the reference preparation, Md AUC_{0-t}= 15.86 ng/ml*h).

The peak serum concentration of oxybutynin after the test controlled release tablet (Md C_{max}= 2.13 ng/ml) was however significantly lower and it was reached significantly later (Md t_{max}= 1.5 h) than those after administration of the reference tablets (Md C_{max}= 6.86 ng/ml, Md t_{max}= 0.75 h). This is also shown in the appended Figures 1 and 2. In these Figures, Fig. 1 shows the mean serum concentration of oxybutynin as a function of time after administartion of a 10 mg controlled release tablet of the invention, and 2 * 5 mg conventional tablets. Fig. 2 shows the serum concentration of the metabolite, N-desethyl oxybutynin after the said administration.

The clinical importance of the extended release pattern of the controlled release tablet was demonstrated by statistically significantly less anticholinergic side-effects compared to the conventional tablet. Furthermore, the high and persistent levels of the active metabolite of oxybutynin for the whole 24 h study period reflects the extended release characteristics of the 10 mg controlled release tablet.

In summary,

1. The controlled release tablet of the invention gave a reliable pharmacokinetic profile of an extended release formulation covering the 24-hour study period.

2. There were no statistically significant differences in the AUC of oxybutynin in serum after administration of the test controlled release tablet compared to that after intake of two 5 mg ordinary tablets.

3. The controlled release tablet can be considered a successful and clinically bioequivalent formulation when lower peak concentrations of oxybutynin in serum are desirable to diminish anticholinergic side-effects of oxybutynin.

Claims:

1. A controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

2. The delivery system according to claim 1, wherein the the ratio of oxybutynin to hydrophilic material is about 1:5 to 1:15.

3. The delivery system according to claim 1 wherein the oxybutynin is in the form of its hydrochloride salt.

4. The delivery system according to claim 3 in the form of a tablet containing from 5 to 20 mg of oxybutynin hydrochloride.

5. The delivery system according to claim 3 in the form of a tablet containing about 10 mg of oxybutynin hydrochloride.

6. A method of making a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising providing a controlled release excipient by combining

- about 15 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1, with

- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight, and with

- about 20 - 79 % by weight of an inert filler,

combining said obtained controlled release excipient with oxybutynin, or a pharmaceutically acceptable salt thereof in an amount as to provide a ratio of oxybutynin to hydrophilic material from about 1:2 to 1:25, and, optionally using pharmaceutically acceptable adjuvants, forming the obtained mixture into a solid dosage form.

7. The method according to claim 6, wherein oxybutinin is used as its hydrochloride salt, the ratio of oxybutynin to hydrophilic material being about 1:5 to 1:15.

8. The method according to claim 7 wherein the mixture is compressed into tablets each containing from 5 to 20 mg, advantageously about 10 mg of oxybutynin hydrochloride.

9. Use of oxybutynin or its pharmaceutically acceptable salt for the preparation of an oral drug delivery system according to claim 1, providing extended and even release of the active agent over a period of time of at least 24 hours, for the treatment of disorders responsive to the effect of an antispasmodically active agent.

10. Use oxybutynin or its salt according to claim 9 for the preparation of a drug delivery system for the treatment of a neurogenic bladder.

11. A method for treating a subject for relief of a condition responsive to the action of an antispasmodically active agent, the method comprising administering to the subject for oral ingestion a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
- about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
- about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

12. The method according to claim 11 wherein the condition to be treated is selected from the group consisting of voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction.

13. The method according to claim 12, wherein the condition to be treated is neurogenic bladder.

14. The method according to claim 11, wherein the delivery system is a tablet containing from about 5 to 20 mg of oxybutynin hydrochloride.

15. The method according to claim 11 wherein oxybutynin hydrochloride is adminstered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

16. A method for maintaining a therapeutically sufficiently high blood level concentration of oxybutynin or of an active metabolite thereof, in a human subject, for an extended period of time, the method comprising administering orally to the subject a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
- about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
- about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

17. The method according to claim 16 wherein the extended period of time is at least about 24 hours.

18. The method according to claim 16 or 17 wherein oxybutynin hydrochloride ia administered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

FIG. 1

THE MEAN CONC. OF OXYBUTYNIN

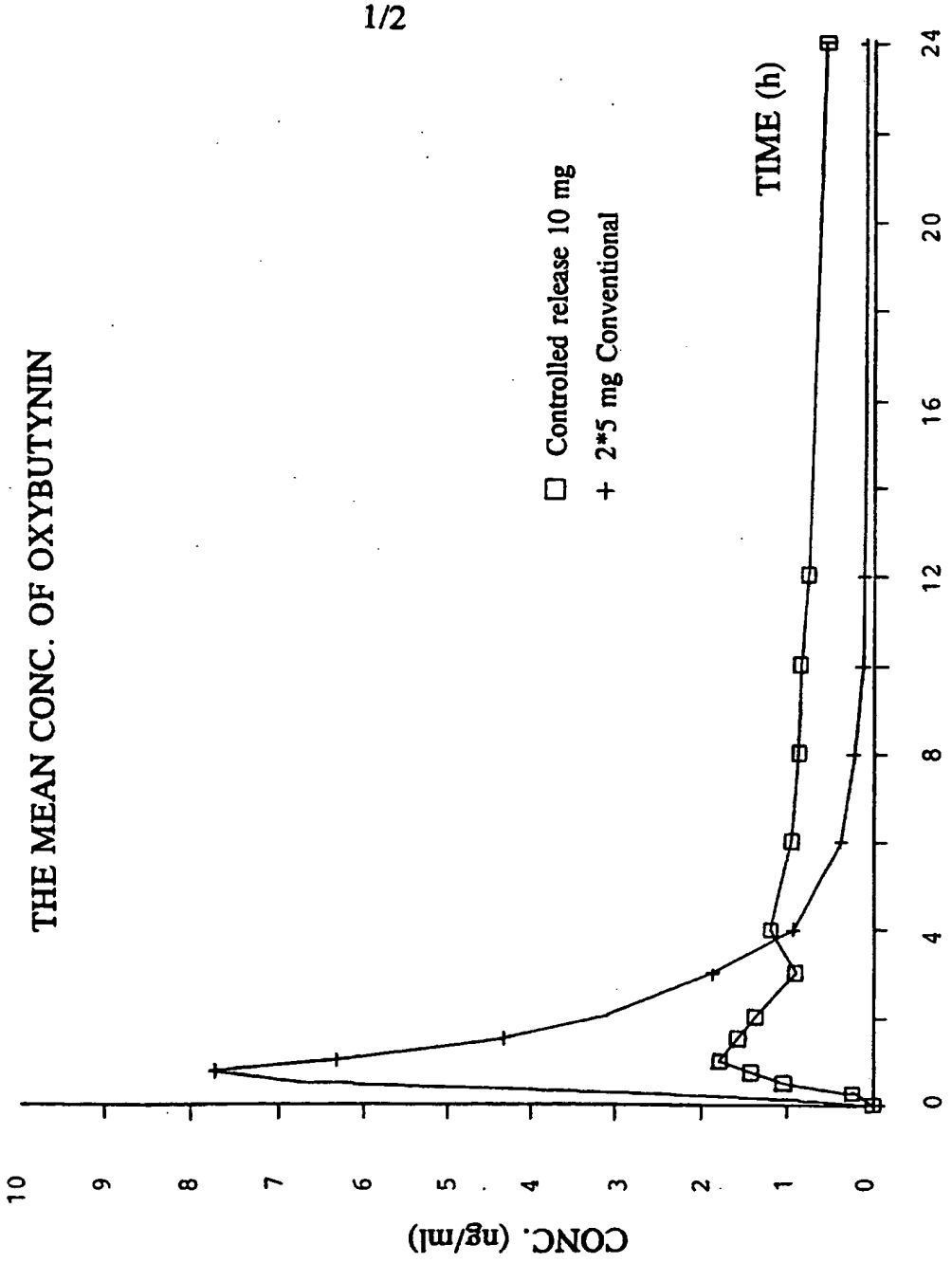
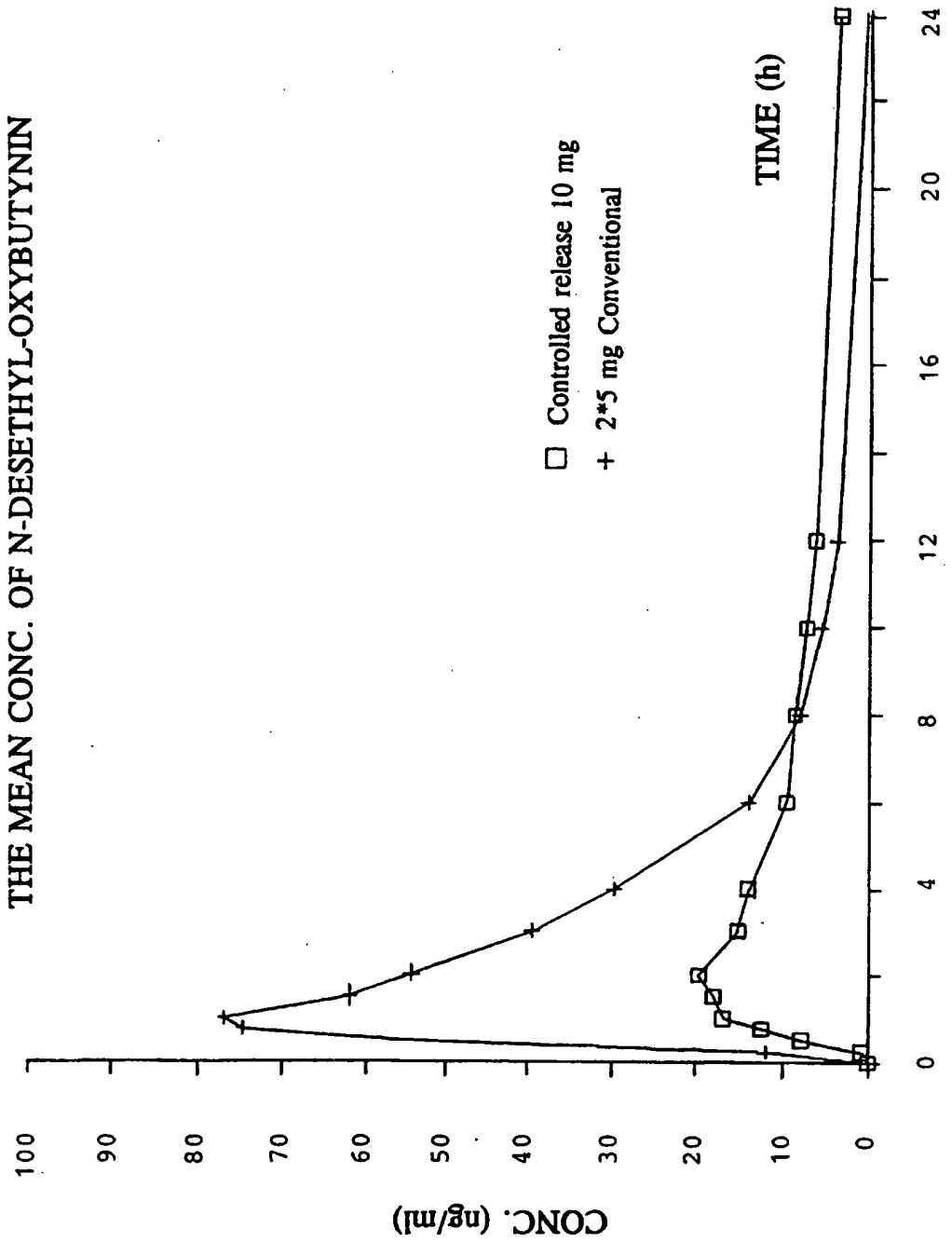


FIG.2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/22, A61K 31/215
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US, A, 5399359 (ANAND R. BAICHWAL), 21 March 1995 (21.03.95) --	1-10
X	US, A, 5169639 (ANAND R. BAICHWAL ET AL), 8 December 1992 (08.12.92), claims --	1-10
X	US, A, 5135757 (ANAND R. BAICHWAL ET AL), 4 August 1992 (04.08.92), column 6, line 49 - column 10, line 9, claims --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1995	13 -06- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0497977 (NIPPON SHINYAKU CO., LTD.), 12 August 1992 (12.08.92), column 7, line 22 - line 27, examples 4-6	1-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/95

International application No.
PCT/FI 94/00474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5399359	21/03/95	NONE	
US-A- 5169639	08/12/92	AU-B- 623182	07/05/92
		AU-A- 4305789	18/04/90
		DE-T- 68907835	11/11/93
		EP-A,A,A 0360562	28/03/90
		SE-T3- 0360562	
		ES-T- 2059778	16/11/94
		JP-T- 4501713	26/03/92
		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
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US-A- 5135757	04/08/92	AU-B- 623182	07/05/92
		AU-A- 4305789	18/04/90
		DE-T- 68907835	11/11/93
		EP-A,A,A 0360562	28/03/90
		SE-T3- 0360562	
		ES-T- 2059778	16/11/94
		JP-T- 4501713	26/03/92
		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
		US-A- 5128143	07/07/92
		US-A- 5169639	08/12/92
		US-A- 5171440	15/12/92
		WO-A- 9003165	05/04/90
EP-A1- 0497977	12/08/92	DE-D- 69017915	00/00/00
		US-A- 5368861	29/11/94
		AT-T- 119766	15/04/95
		WO-A- 9106281	16/05/91

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agents: LEMACK, Kevin, S. et al.; Nields, Lemack & Dingman, Suite 8, 176 E. Main Street, Westboro, MA 01581 (US).

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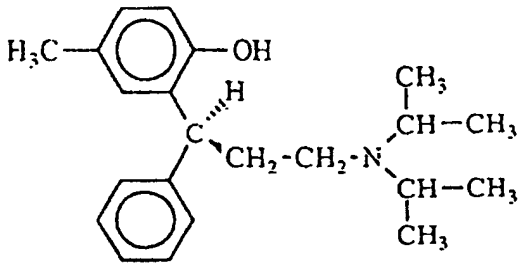
Published
With international search report.

(54) Title: S(-)-TOLTERODINE IN THE TREATMENT OF URINARY AND GASTROINTESTINAL DISORDERS

(57) Abstract

The S-isomer of a compound represented by formula (I) and pharmaceutically acceptable salts thereof is disclosed as being useful for treating urinary disorders, including urinary incontinence, and gastrointestinal disorders, including gastrointestinal hyperactivity.



(I)

S(-)-tolterodine

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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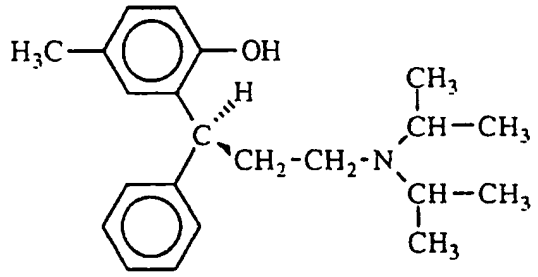
S(-)-TOLTERODINE IN THE TREATMENT OF URINARY AND GASTROINTESTINAL DISORDERS

FIELD OF THE INVENTION.

This invention relates to a compound named S(-)-tolterodine and having the formula:



S(-)-tolterodine

Specifically, the invention relates to processes for preparing S-tolterodine. to a method for treating urinary disorders, including urinary incontinence and a method for treating gastrointestinal disorders, including gastrointestinal hyperactivity, using the compound S-tolterodine and to pharmaceutical compositions containing S-tolterodine.

The generic name TOLTERODINE (CAS-124937-51-1; INN) refers to the R-enantiomer of the drug. In this document. the racemate and the optically active isomers of the compound are referred to as RS-tolterodine (or RS-TOL), S-tolterodine (or S-TOL), and R-tolterodine (or R-TOL).

BACKGROUND OF THE INVENTION.

R-tolterodine has been shown to reduce bladder pressure in cats and is presently undergoing clinical testing for inhibitory activity in patients suffering from detrusor overactivity (urinary incontinence). R-TOL exerts a spasmolytic effect on bladder smooth muscle by inhibiting the action of acetylcholine on smooth muscle. R-TOL is selective for muscarinic receptors over nicotinic receptors and as a result, no blocking

effects are observed at skeletal neuromuscular junctions. Like all other antimuscarinic compounds, R-TOL causes dry mouth, blurry vision, tachycardia and possibly also memory impairment.

R-TOL relaxes urinary bladder smooth muscle and in animals with conditions characterized by increased bladder contractions, cystometric studies have demonstrated that R-TOL has beneficial effects. R-TOL may therefore be useful in the treatment and prevention of incontinency and frequent voluntary urination in patients. The efficacy of R-TOL in the bladder has been attributed to its antimuscarinic effects on the detrusor muscle. Because of its antimuscarinic activity, mydriasis (dilated pupils), xerostomia (dry mouth), tachycardia (fast heart beats) and impaired normal urinary voiding, which mechanisms all involve muscarinic cholinergic receptors, are obvious and reported side effects for R-TOL (Ekström et al., J. Urol. 1995, Suppl.4: 394A and Stahl et al. 1995, Neurourol Urodyn.14: 647-655).

Pharmacological studies of the individual enantiomers of tolterodine have now been performed and have suggested that the R-TOL indeed is the efficacious enantiomer on muscarinic receptors. Thus, it was concluded that the cholinergic antagonism of racemic tolterodine (RS-TOL) could be attributed mainly to the activity of R-TOL. The rank order of potency of racemic tolterodine and its enantiomers for antimuscarinic activity is: R-TOL was greater or equal to RS-TOL, which was much greater than S-TOL, with S-TOL being approximately one or more orders of magnitude less potent than R-TOL.

SUMMARY OF THE INVENTION

It has now unexpectedly been found that S-TOL has outstanding non-cholinergic spasmolytic activities, while being practically devoid of anticholinergic activity. It has furthermore unexpectedly been found that S-TOL provides weak sedative effects. S-TOL therefore will offer superior treatment for urinary disorders, including urinary incontinence and for gastrointestinal disorders, including gastrointestinal hyperactivity, while being devoid of the anticholinergic side effects that reside in R-TOL.

While the optically pure R-TOL provides medical treatment in patients with urinary incontinence that arises from one single cause, namely muscarinic hyperactivity, it was found that the optically pure S-TOL provides spasmolytic activity against urinary and intestinal spasms that arise from various mechanisms. S-TOL is particularly useful in patients where urinary incontinence is caused by non-cholinergic mechanisms or in patients, where antimuscarinic side effects are not acceptable (for example in the elderly, where antimuscarinic side effects have unacceptable effects on memory). Non-cholinergic spasmogenic mechanisms include but are not limited to scars (i.e. from childberth or surgical interventions) causing detrusor pacemaker activity, release of thromboxane, release of platelet activating factor and other non-muscarinic spasmogens.

Chemically, S-TOL is S(-)-2-[α[2-(diisopropylamino)ethyl] benzyl]-*p*-cresol.

The active compound of this invention is S-TOL. The synthetic preparation is described in European Pat. Appl. EP 325571 A1, the disclosures of which are hereby incorporated by reference.

Alternatively, S-TOL can be prepared by stereoselective synthesis, using (other) chiral templates.

Alternatively, S-TOL can be obtained by the resolution of RS-TOL using conventional means such as fractional crystallization of diastereomeric salts with chiral acids. Other standard methods of resolution known to those skilled in the art, include, but are not limited to, crystallization and chromatography on a chiral substrate and can also be used.

The magnitude of a prophylactic or therapeutic dose of S-TOL in the acute or chronic management of disease will vary with the severity and nature of the condition to be treated and the route of administration. The dose and the frequency of the dosing will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for S-TOL for the conditions described herein is from about 0.5 mg to about 100 mg in single or divided doses, preferably in divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 0.5 mg to about 25 mg, and may be increased up to about 200 mg depending on the patient's global response.

It is further recommended that patients over 65 years and those with impaired renal or hepatic function initially receive low doses and that they be titrated based on individual response(s) and plasma drug level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat the disorder but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of S-TOL. For example, oral, sublingual, parental (i.e. subcutaneous, intramuscular, intravenous, etc.), transdermal, vaginal, aerosol and like forms of administration may be employed. Additionally, the drug may be administered directly into the bladder, as described for oxybutynin by Massad et al. [J. Urol. 148. 595-597 (1992)] or rectally directly into the gastrointestinal canal as known in the art. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, suppositories, microencapsulated systems, slowrelease and controlled release systems, transdermal delivery systems, and the like.

The pharmaceutical compositions of the present invention comprise of S-TOL as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, p-toluenesulfonic, succinic, sulfuric, tartaric, and the like. The hydrochloride is particularly preferred.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the more advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and delivery devices such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, and PCT application WO92/20377, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete unit dosage forms such as capsules, cachets, suppositories, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation, just as is known for the racemic mixture.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert

liquid diluent. All of the foregoing techniques are well know to persons of skill in the pharmaceutical art. Each tablet may contain from about 0.5 mg to about 25 mg of the active ingredient.

EXAMPLES

Example 1

ORAL UNIT DOSAGE FORMULATION

Tablets:

Ingredients	per tablet	per batch of 10,000 tablets
S-TOL	5 mg	50 g
Microcrystalline cellulose	30 mg	300 g
Lactose	70 mg	700 g
Calcium stearate	2 mg	20 g
FD&C Blue #1 Lake	0.03 mg	300 mg

The S-TOL is blended with lactose and cellulose until a uniform blend is formed. The lake is added and further blended. Finally, the calcium stearate is blended in, and the resulting mixture is compressed into tablets using a 9/32 inch (7 mm) shallow concave punch. Tablets of other strengths may be prepared by altering the ration of active ingredient to the excipients or to the final weight of the tablet.

Example 2.

Pharmacological Studies of S-TOL, RS-TOL or R-TOL

1. Ligand Binding Studies: Muscarinic Receptors.

The experimants are carried out on membranes prepared from SF9 cells infected with baculovirus to express human recombinant muscarinic receptor subtypes. After incubation with the test article and the proper radioligand and washing, bound radioactivity is determined with a liquid scintillation counter, using a commercial scintillation cocktail. The specific radioligand binding to each receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabelled ligand. IC_{50} values (concentrations required to inhibit 59% of specific binding) are determined by non linear regression analysis of the competition curves. These parameters are obtained by curve fitting using Sigmaplot™ software.

2. Functional Characterization of Antimuscarinic/Antispasmodic Activity.

Bladder and intestinal smooth muscle strips. Experiments are performed using methods similar to those described by Kachur et al, 1988 and Noronha-Blob and Kachur, 1991. Strips of tissue (approximately 10 mm long and 1.5 mm wide) are removed from the body of the urinary bladder of male Hartley guinea pigs weighing 400-600 g. Preparations of the longitudinal smooth muscle of the colon of guinea pigs are prepared as known in the art (Acta Physiol Scand 64: 15-27, 1965). The tissues are suspended in an oxygenated buffer of the following composition, in mM: NaCl, 133; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 0.6; NaH_2PO_4, 1.3; $NaHCO_3$, 16.3; and glucose, 7.7, or of a similar composition. They are maintained at 37.5 C. Contractions are recorded with isometric transducers (Model FT-10) on an ink-writing polygraph.

In each experiment up to seven strips are removed from a single animal, suspended in tissue chambers and allowed to equilibrate with the bathing solution for one hour before proceeding with the experiment.

Contractions induced by carbachol. One series of experiments focuses on the anticholinergic actions of S-TOL, RS-TOL or R-TOL. In these experiments, in order to assess the viability of each tissue and to serve as a frame of reference, contractions of each strip of tissue are recorded initially in response to exposure to tissue medium in which the NaCl was replaced by KCl to yield a concentration of 137.7 mM KCl in the medium. This is followed by return to the standard medium, and then by exposures to progressively in creasing concentrations of carbachol, with separate exposures to each concentration only until the peak response has been recorded. Then, leaving one strip untreated and/or one strip exposed to the test solution to serve as control tissue(s), the remaining strips each are exposed for one hour to one concentration of an antagonist. Finally, the responses to increasing concentrations of carbachol followed by exposure to 137.7 mM KCL are recorded a second time.

Contractions induced by hig potassium concentration. A second series of experiments focuses on the spasmolytic action of the substances being studied against high concentrations of K^+. Contractions in response to sequentially increasing the concentration of potassium in the medium are recorded.

Contractions induced by other spasmogens. A third series of experiments focuses on spasmolytic activities against other spasmogens. The contractions are recorded in response to sequentially increasing the concentration of such spasmogens in the medium.

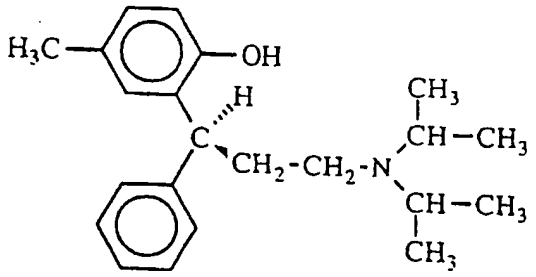
Data analysis. To determine whether antagonists decrease the peak response to agonists, the peak tension developed by each strip during the second set of determinations is expressed as a percent of the peak tension developed during the first concentration-effect determination. Then, for each antagonist the resultant data are analyzed for treatment-related differences by one-way analysis of variance (ANOVA). Since only one concentration of antagonist is studied in each strip of bladder, a modified procedure is used to estimate the pA2 and slope of the Schild regression. First, the concentrations of agonist producing a half-maximal response (the EC_{50}) is estimated for each strip from the second set of concentration-effect data. The EC_{50} is obtained from linear regression lines fit to the logarithm of the concentration of drug and the responses bracketing the half maximum level of response. For each drug-treated strip, a "concentration ratio" (CR) is calculated as the ratio of the EC_{50} of the treated tissue divided by the EC_{50} of the untreated tissue. For each experiment where two or more strips are exposed to the same chemical

but at different concentrations, the logarithm of this ratio minus one [i.e., log (CR-1)] is plotted against the logarithm of the concentration of antagonist to which the strip had been exposed to produce "Schild plots". A regression analysis relating log(CR-1) to the logarithm of the concentration of the antagonist is employed to estimate the pA2 and the slope of the regression line. Finally, experiments are grouped by chemical and the mean ± S.E.M. of the pA2 and slope are calculated.

Since S-TOL exhibits significantly decreased anticholinergic side effects as compared with the corresponding R-isomer and racemate, administration of S-tolterodine will allow avoidance of parasympathec cardiovascular side effects (i.e. tachycardia etc.) and other parasympathetic side effects (i.e. dry mouth, blurry vision, inhibition of normal urinary voiding mechanisms etc.), and the avoidance of memory loss that arise from the anticholinergic action of R-TOL. It is now therefore concluded that S-TOL is an effective medicament for the treatment of urinary voiding disorders, including urinary incontinence, and for the treatment of gastrointestinal disorders, including gastrointestinal hyperactivity in humans with greatly reduced side effects over the corresponding racemate or the pure R-enantiomer.

CLAIMS.

1. S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol. having the formula:



and pharmaceutically acceptable salts thereof.

2. A method for treating urinary voiding disorders , including incontinence, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol and pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

3. A method for treating gastrointestinal disorders. including gastro-intestinal hyperactivity, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol and pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

4. The method for treating urinary voiding disorders , including incontinence, while reducing concomitant liability of adverse effects associated with racemic tolterodine or the R-enantiomer of tolterodine, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salts thereof. substantially free of its R enantiomer.

5. The method for treating gastrointestinal disorders, including gastrointestinal hyperactivity, while reducing concomitant liability of adverse effects associated with racemic tolterodine or the R-enantiomer of tolterodine, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salts thereof, substantially free of its R enantiomer.

6. The method of claim 4 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

7. The method of claim 5 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered by inhalation or by parenteral, transdermal, rectal, sublingual or oral administration.

8. The method of claim 4 wherein the amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered from about 0.5 mg to about 200 mg per day.

9. The method of claim 5 wherein the amount of S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol or a pharmaceutically acceptable salt thereof is administered from about 0.5 mg to about 200 mg per day.

10. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol. or a pharmaceutically acceptable salt thereof, is administered orally.

11. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol. or a pharmaceutically acceptable salt thereof, is administered orally.

12. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally in an extended release formulation.

13. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered orally in an extended release formulation.

14. The method according to claim 4 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered transdermally.

15. The method according to claim 5 wherein S(-)-2-[α-[2-(diisopropylamino) ethyl]benzyl]-p-cresol, or a pharmaceutically acceptable salt thereof, is administered transdermally.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/741

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS
search terms: tolterodine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NILVEBRANT, L. Tolterodine--A New Baldder Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological Data. Life Sciences. 1977, Vol . 60, pages 1129-1136.	1-15
X	NILVEBRANT, L. Tolterodine-- A New Bladder Selective Antimuscarinic Agent. Eur. J. Pharmacol. 1977, Vol. 327, pages 195-207.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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(54) Title: THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

(57) Abstract

A method and formulation for treating unstable or overactive urinary bladder, wherein tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, is administered to a patient in a pharmaceutically effective amount thereof through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours.

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THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533-542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

Recently, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195-207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647-655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287-295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

In one aspect, the present invention therefore provides a method of treating unstable or overactive urinary bladder, which method comprises administering to a (mammal) patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a

controlled rate for at least 24 hours. It is preferred that the dosage form formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The term "tolterodine-related compound" is meant to encompass the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms thereof.

By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation

should essentially not exhibit any peak values. This may, more sophistically, also be expressed by reference to the "flucuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. Thus, according to the present invention, the controlled release formulation should provide a mean fluctuation index (for n being at least 30) that is usually not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the

(S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

In another aspect, the present invention provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

Still another aspect of the present invention provides the use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides a controlled release of tolterodine or said tolterodine-related compound, or salt thereof at a controlled rate for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

The controlled release formulation is preferably an oral delivery system or a transdermal preparation, such as a transdermal patch, but also other controlled release forms may, of course, be contemplated, such as buccal tablets, rectal suppositories, subcutaneous implants, formulations for intramuscular administration.

An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case

of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer).

In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine (or tolterodine related compound) is, for example, 4 mg or 6 mg.

A transdermal patch for tolterodine or tolterodine-related compound is described in our co-pending international application "Transdermally administered tolterodine as antimuscarinic agent for the treatment of overactive bladder" (based on Swedish patent application no. 9802864-0, filed on 27 August 1998), the full disclosure of which is incorporated by reference herein. Illustrative patch formulations are described in Example 2 below.

With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules, patches etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

The invention is illustrated by the following Examples, without, however, limiting the scope of the invention in any way. Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

Figure 1 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

Figure 2 is a diagram showing the variation of the basal salivation (g/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

Figure 3 is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of tolterodine CR capsules 2 mg and 4 mg

A controlled release (CR) capsule containing non-pareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

- (1) a Surelease® sealcoating solution prepared by mixing 788 g of Surelease® with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, PA, U.S.A.);
- (2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5cP (hydroxypropylmethyl cellulose (HPMC)); and

- (3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169-207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	69 mg	137 mg
Surelease®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-tartrate IR tablets 2 mg

Commercially available tolterodine L-tartate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core	
Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg
Coating	
Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanum dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum concentrations of tolterodine and main metabolite

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136). Figure 1 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet

twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI = (Cmax - Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95-2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59-0.78) for the TOD capsule.

Salivation (dry mouth)

Salivation was measured using dental cotton rolls applied in the mouth for 3 x 2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in Figure 2. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

While Fig. 2 shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in Figure 3.

The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

As apparent from Fig. 2, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

The results from the salivation determinations thus show that flattening of the concentration peaks of the "active moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual urine volume

Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

Table 1

Mean Residual Volume per micturition (ml)

	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			-22	-4	7	14
			-44 to 1	-23 to 15	-13 to 26	-7 to 36

Table 2

Maximum Residual Volume during 12 hours

	Placebo	TIR 2mg b.i.d	TOD 2mg	TOD 4mg	TOD 6mg	TOD 8mg
Median value (ml)	46	72	45	55	87	77
min-max	5-267	10-316	0-192	0-349	0-360	0-390

The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

EXAMPLE 2

TOLTERODINE TRANSDERMAL PATCH FORMULATION

Tolterodine-releasing patches were prepared as follows:

System 1 (drug-in-adhesive, acrylate)

5 g of tolterodine base were dissolved in 11 g of ethanol and added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel was coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) by using a coating equipment (RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness was 400 µm. The laminate was dried for 20 min. at RT and then for 30 min. at 40°C. A polyester release liner (S 2016; Rexam Release) was laminated onto the dried drug gel. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,5 mg/cm².

System 2 (multi-laminate, acrylate)

5 g of tolterodine base were dissolved in 10 ml of ethanol. A mix of 6,4 g of Eudragit RL 100 (Röhm GmbH Chemische Fabrik, Germany) and 6,4 of ethanol and a mix of 2,6 g of Polyvidone 90 (BASF, Germany) and 10,2 g of ethanol were added to the solution of tolterodine base in ethanol. Finally, 4 g of propylene glycol were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment above. The wet layer thickness was 400 µm. The laminate was then dried at 40°C for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80°C for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,0 mg/cm².

System 3 (multi-laminate, water-based acrylate)

1 g of tolterodine base was mixed with Tween 80 (Merck) by heating to 60 - 70°C. 1,8 g of triethylacetate and 1,3 g of dem. water was added to the mix. The final mix was then added to 25 g of Eudragit RL 30 D (Röhm GmbH Chemische Fabrik, Germany). Finally, 180 mg of 1 N NaOH

were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment. The wet layer thickness was 400 µm. The laminate was dried at 40°C for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80°C for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2-8°C until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 0,5 mg/cm².

CLAIMS

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours.

2. The method according to claim 1, wherein the formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

3. The method according to claim 2, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

4. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

5. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum

level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

6. The method according to any one of claims 1 to 5, wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

7. The method according to any one of claims 1 to 5, wherein the controlled release formulation is a transdermal preparation, preferably a transdermal patch.

8. The method according to any one of claims 1 to 7, wherein tolterodine is administered.

9. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

10. The formulation according to claim 9, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound

tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

12. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

13. The formulation according to any one of claims 9 to 12, which is a capsule or tablet for oral administration once daily.

14. The formulation according to any one of claims 1 to 12, which is a transdermal preparation, preferably a transdermal patch.

15. The formulation according to any one of claims 9 to 14, which provides controlled release of tolterodine.

16. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

17. The use according to claim 16, wherein a formulation according to any one of claims 10 to 15 is manufactured.

18. A method for providing a continuous plasma concentration of tolterodine-related active moiety in a patient, wherein the method comprises administering a

dosage form formulation comprising tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, that is administered over at least 24 hours to the patient at a controlled and sustained rate to provide the desired plasma active moiety concentration.

19. The method according to claim 18, wherein the dosage form formulation is administered orally.

AMENDED CLAIMS

[received by the International Bureau on 10 February 2000 (10.02.00);
original claims 1-19 replaced by new claims 1-17 (3 pages)]

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours.

2. The method according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. The method according to claim 1 or 2, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

4. The method according to claim 1, 2 or 3, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

5. The method according to any one of claims 1 to 4, wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The method according to any one of claims 1 to 4, wherein the controlled release formulation is a transdermal preparation, preferably a transdermal patch.

7. The method according to any one of claims 1 to 6, wherein tolterodine is administered.

8. The method according to any one of claims 1 to 6, wherein urinary incontinence is treated.

9. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

10. The formulation according to claim 9, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the 24-hour serum profile, expressed as the AUC of

unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

12. The formulation according to claim 9 or 10, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

13. The formulation according to any one of claims 9 to 12, which is a capsule or tablet for oral administration once daily.

14. The formulation according to any one of claims 1 to 12, which is a transdermal preparation, preferably a transdermal patch.

15. The formulation according to any one of claims 9 to 14, which provides controlled release of tolterodine.

16. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

17. The use according to claim 16, wherein a formulation according to any one of claims 10 to 15 is manufactured.

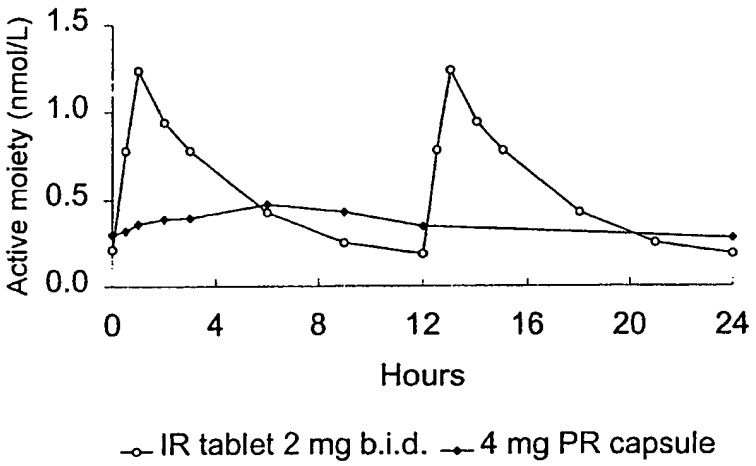
Active moiety (nmol/L)
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 1

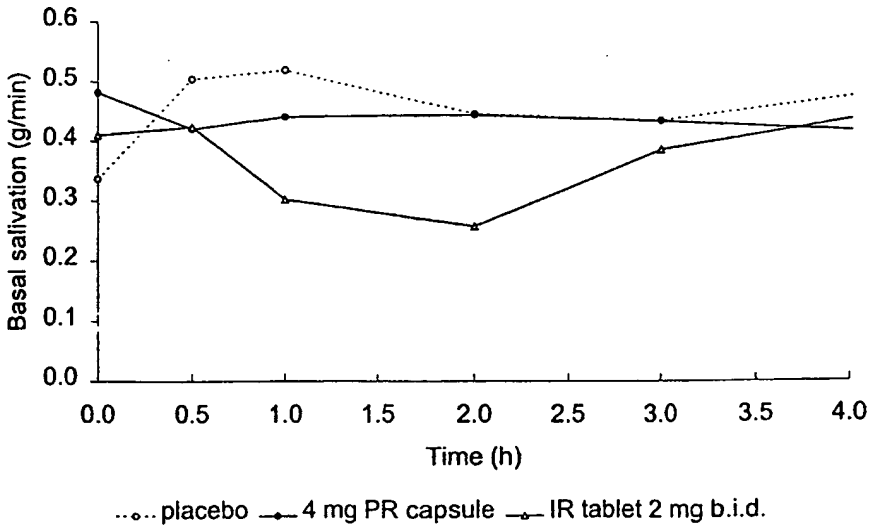
Basal salivation (g/min)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (h)
placebo
4 mg PR capsule
IR tablet 2 mg b.i.d.

FIG. 2

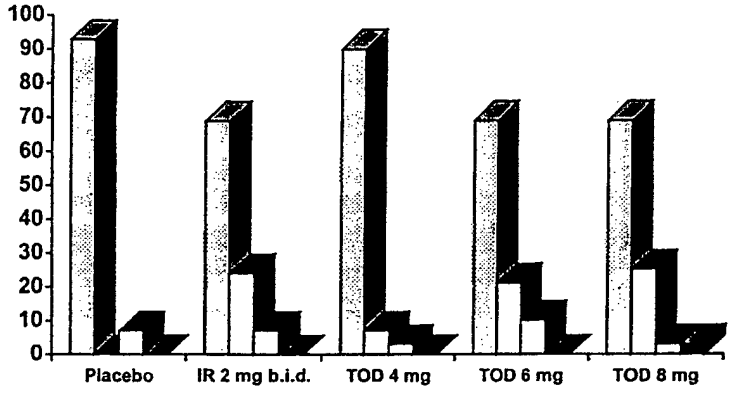

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/22, A61K 9/52, A61K 9/70, A61K 31/135, A61P 13/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9803067 A1 (ÅBERG, GUNNAR), 29 January 1998 (29.01.98), abstract, second paragraph on page 4, third paragraph on page 5 and claims 12 and 13	1-19
A	WO 9811888 A1 (AMERICAN HOME PRODUCTS CORPORATION), 26 March 1998 (26.03.98), page 3, line 5; page 3, line 20 - line 25	1-19
A	WO 9612477 A1 (LEIRAS OY), 2 May 1996 (02.05.96)	1-19
A	WO 9323025 A1 (ALZA CORPORATION), 25 November 1993 (25.11.93)	1-5,7-12, 14-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 1999	19 January 2000 (19.01.00)
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson / MR Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8, 18-19
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01463

Remark: Claims 1-8,18-19 are directed to methods of treatment of the human or animal body by terapy methods practised on the human or animal body/Rule 39.1(iv) Nevertheless a search has been executed for these claims. The search has been based on the alleged effects of the copositions.

INTERNATIONAL SEARCH REPORT

02/12/99

International application No.
PCT/SE 99/01463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803067 A1	29/01/98	AU 3725997 A	10/02/98
		CA 2259012 A	29/01/98
		EP 0924983 A	30/06/99
WO 9811888 A1	26/03/98	AU 4421697 A	14/04/98
		EP 0927034 A	07/07/99
WO 9612477 A1	02/05/96	AU 7994694 A	15/05/96
WO 9323025 A1	25/11/93	AT 185694 T	15/11/99
		AU 666735 B	22/02/96
		AU 4247393 A	13/12/93
		CA 2132865 A	25/11/93
		DE 69326848 D	00/00/00
		EP 0767659 A,B	16/04/97
		FI 945311 A	11/11/94
		JP 8502952 T	02/04/96
		MX 9302812 A	01/11/93
		NO 944249 A	14/11/94
		NZ 252598 A	29/01/97
		US 5411740 A	02/05/95
		US 5500222 A	19/03/96
		US 5900250 A	04/05/99
		ZA 9303349 A	15/06/94

Form PCT/ISA/210 (patent family annex) (July 1992)

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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PCT/SE99/01463	26 August 1999 (26.08.99)	SE

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Published
With international search report.

(54) Title: NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT

(57) Abstract

A controlled release bead comprises: (i) a core unit of a substantially water-soluble or water-swellable inert material; (ii) a first layer on the core unit of a substantially water-insoluble polymer; (iii) a second layer covering the first layer and containing an active ingredient; and (iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient, wherein the first layer is adapted to control water penetration into the core. A method of producing the controlled release bead is also disclosed.

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NEW CONTROLLED RELEASE BEAD, A METHOD OF PRODUCING THE SAME AND MULTIPLE UNIT FORMULATION COMPRISING IT

The present invention relates to pharmaceutical controlled release beads comprising a drug, to a formulation containing said controlled release beads, and to a method of preparing said beads.

A common type of controlled release beads comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer.

An example of such controlled release beads is described in US-A-5,783,215 where each bead comprises (i) a core unit of a soluble or insoluble inert material, (ii) a first layer on the core unit comprising an active ingredient dispersed in a hydrophilic polymer, (iii) an optional second layer of hydrophilic polymer covering the first layer, and (iv) an outermost membrane layer effective for controlled release of the active ingredient.

In the above and similar controlled release beads it is not uncommon to apply a "sealcoat" in the form of a small amount (e.g. 1-3%) of a water-soluble polymer, such as hydroxypropylmethyl cellulose (HPMC) or polyvinylpyrrolidone (PVP), between the inert core and the layer containing the active ingredient. The purpose thereof is generally to isolate the drug from the core surface in the event that a drug-core chemical interaction is possible, and/or to smooth the surface of the inert core such that the surface area is more consistent from lot to lot to thereby improve the coating quality when the drug layer and the controlled release membrane layers are applied.

According to the present invention, it has now surprisingly been found that by applying a relatively thick layer of a water-insoluble polymer to the inert core as a sealcoat, several advantages may be obtained in addition to those mentioned above.

Firstly, in case of a soluble core like one of sugar, for example, the amount of time that the solution within the bead would be saturated with respect to drug may be maximized. Thus, by preventing the soluble core from being a reservoir for drug dissolution, the relative time that a saturated solution would remain within the bead during the release period can be increased considerably. This means that a substantially longer zero order drug release phase (the phase when the drug release rate is essentially

constant) will be obtained (and less in the undesirable declining release rate phase). In other words, generally, the use of a thick sealcoat layer will permit the drug release profile to be altered in a predictable fashion, in particular for drugs with a moderate to high water solubility. Also, without drug migrating into the sealcoat, all drug will get released.

Secondly, the potential influence of the core material on drug release, in particular osmotic pressure or swelling of the core material which could potentially cause internal pressure and film rupture, may be minimized.

Thirdly, the substantial initial lag phase (no or very low amount of drug release early) that is generally observed with the prior art controlled release beads, especially for slower release formulations where the water influx is slower, may be substantially reduced or eliminated relatively independently of the steady state release rate.

Therefore, in a first aspect, the present invention provides a controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material having;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-

thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

In a second aspect, the present invention provides a multiple unit formulation comprising said controlled release beads, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. Especially, the beads are spheres of sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (latex or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

A wide variety of therapeutically active agents may be used in conjuction with the present invention. While the therapeutic agent usually is a low or medium dose drug, also high-dose drugs may be contemplated for use in the present invention. The therapeutic agent is preferably a soluble or moderately water-soluble drug (e.g. having a solubility corresponding to from less than 1 to about 30 ml of water per gram of solute at a temperature between 15 °C and 25 °C).

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer,

or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

In a third aspect, the present invention provides a method for producing the controlled release beads and formulation, respectively. This method comprises the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, the method comprises the further step of applying one or more additional polymer layers to the core as has been mentioned above.

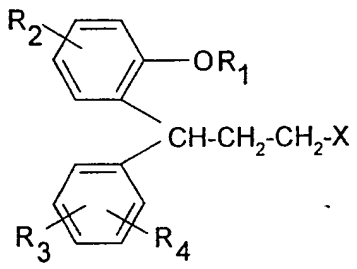
The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

The pharmaceutical formulation of the invention may be administered orally.

An exemplary class of compounds which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 (the entire diclosures of which are incorporated by reference herein) and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. An exemplary specific compound is tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

Useful analogues to the above compounds are disclosed in WO 98/43942 (the full diclosure of which is incorporated by reference herein).

The above as well as the latter compounds have anti-cholinergic activity and may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial

cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The compounds also have spasmolytic activity and may be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

Specifically, the beads and multiple unit formulation, respectively, according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urge incontinence, urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine. A salient feature of tolterodine is that it has considerably less side-effects than the previously conventionally used drug, oxybutynin, especially regarding the propensity to cause dry mouth.

When tolterodine is the active ingredient in the controlled release bead, the fraction of active ingredient that is released in vitro is preferably not more than about 30% after 1 hour, from about 40 to about 85% after 3 hours, and not less than about 80% after 7 hours.

Administration of the controlled release formulation according to the present invention permits a well controlled release of tolterodine, and thereby a substantially constant serum level of active moiety or moieties to be maintained in the patient for at least 24 hours.

By the term "active moiety or moities" is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations

of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite)

are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with different sealcoat thicknesses; and

Fig. 2 is a diagram showing the fraction of released drug versus time for tolterodine beads according to Example 1 below with 14 % (w/w) and 0 % (w/w) seal coat, respectively. The polymer composition in the third layer of the beads with 0 % sealcoat has been adjusted in order to produce approximately similar initial drug release as from beads with 14 % sealcoat.

EXAMPLE 1

An exemplary bead containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;
First layer:	Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead;

purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;

Second layer: Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1;
purpose: drug supply;

Third layer: Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1;
purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer : HPMC; comprises about 1 % w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Study of effect of sealcoat thickness

The effect of the sealcoat thickness on drug release was tested as follows.

Four lots of 20-25 mesh beads were prepared that contained (i) a Surelease® sealcoat layer at 0, 2, 10 or 14% level, (ii) an HPMC/drug (tolterodine L-tartrate) layer at 4% level (drug:HPMC ratio =5:4), (iii) a Surelease®/HPMC layer at 10% level (Surelease®:HPMC ratio = 6:1 ratio), and (iv) a final HPMC layer at 1%. These were prepared essentially as described above and cured 1 hr at 70 °C.

Note that the coating level for layer (i) is expressed relative to the sum of the core plus sealcoat while coating levels for layers (ii-iv) are expressed relative to the final coated bead weight.

A fifth lot of beads was also manufactured identical to the 0% sealcoat lot described above except that the third coating layer was modified (increase in the Surelease®: HPMC layer from a 6:1 to a 11:1) such that the initial drug release rate was similar to the 14% sealcoat formulation described above.

The in vitro drug release at 37°C in phosphate buffer pH 6.8 with addition of 0.22M potassium chloride was measured. The USP dissolution test apparatus 1 was used. The results are shown in the diagrams in Fig. 1 and 2. As shown in Fig. 1, as the sealcoat layer gets thicker, the drug release rate both decreases and becomes more zero-order.

Fig. 2 shows the comparison of the 0% sealcoat formulation (11:1 Surelease®: HPMC) to the 14% sealcoat (6:1 the Surelease®: HPMC). It can be seen that, after a slight lag period observed by the 0% sealcoated beads, the initial drug release rates are similar. However, after approximately 15-20% of the drug is released, the release rate from beads with 0 % sealcoat beads falls while release rate from the 14% sealcoat remains extremely zero order. Indeed, for the 0 % sealcoat beads the release rate between 45-60% is only approximately half of the initial (first 20 %) release rate. Comparatively, for the 14% sealcoat lot, the release rate between 45-60% range is identical to the rate over the first 20%.

In an analogous manner to the procedure described in Example 1 above, other exemplary bead formulations containing tolterodine L-tartrate as the active ingredient were prepared as described in Examples 2 and 3 below.

EXAMPLE 2

400 g of sugar spheres (20-25 mesh, Edward Mendell Co, USA) were charged into a top-spray fluid bed coater (Nica, Sweden) and coated with Surelease® and thereafter cured in a drying cabinet at 70°C for 5 hours.

A solution of tolterodine-L-tartrate and hydroxypropyl cellulose (HPC) in water was sprayed onto the coated cores.

The spheres obtained were then coated with a mixture of ethylcellulose, hydroxypropylcellulose and triethylcitrate (plasticizer). The coating materials were dissolved in a mixture of dichlormethane and ethanol.

The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	75.7
Surelease®	13
Tolterodine L-tartrate	4.9
HPC	1.5
Ethylcellulose	4.3
Triethyl citrate	0.6

The obtained spheres showed extended release of tolterodine L-tartrate over at least 10 hours. The release rate was essentially constant.

EXAMPLE 3

4800 g of sugar spheres (18-20 mesh, Mendell, USA) were coated in a Wurster fluid bed with Surelease® to a theoretical weight gain of 10 % and thereafter cured in a drying cabinet at 60°C for 6 hours.

A solution of tolterodine L-tartrate and hydroxypropylmethyl cellulose (HPMC) in water was sprayed onto 1200 g of the cured sphere cores.

1000 g of the obtained spheres were then coated by spraying with an aqueous dispersion of a cross-linked latex of hydroxyl-end blocked polydimethylsiloxan (PDMS, Dow Corning; USA) and colloidal silica (Dow Corning, USA) to a theoretical weight gain of 15 %.

The resulting beads had the following composition expressed as % (w/w):

Sugar spheres	76
Surelease®	7.8
Tolterodine L-tartrate	2.8
HPMC	0.4
PDMS	8.7
Colloidal silica	4.3

The obtained spheres showed extended release of tolterodine L-tartrate over at least 11 hours. The release rate was nearly constant.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow.

CLAIMS

1. A controlled release bead comprising:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient,

wherein said first layer is adapted to control water penetration into the core.

2. The bead according to claim 1, wherein the amount of polymer in said first layer is sufficient to substantially retard water penetration into the core.

3. The bead according to claim 1 or 2, wherein the thickness of said first layer is sufficient to affect the drug release rate from the bead.

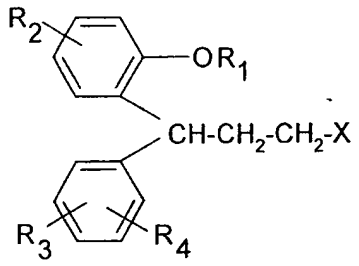
4. The bead according to claim 1, 2 or 3, wherein the amount of the first layer constitutes more than 2% (w/w), preferably more than 3% (w/w) of the final bead composition.

5. The bead according to any one of claims 1 to 4, wherein the amount of said second layer usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

6. The bead according to any one of claims 1 to 5, wherein the amount of said third layer usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

7. The bead according to any one of claims 1 to 6, wherein said third polymer layer is coated with a fourth layer of a water-soluble polymer or an additional functional coating.

8. The bead according to any one of claims 1 to 7, wherein said active ingredient is selected from compounds having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-NR_5,R_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

9. The bead according to claim 8, wherein said active ingredient is selected from tolterodine, the 5-hydroxymethyl metabolite of tolterodine, the (S)-enantiomer of tolterodine, the 5-hydroxymethyl metabolite of the (S)-enantiomer of tolterodine, the racemate of tolterodine, and prodrug forms and pharmacologically acceptable salts thereof.

10. The bead according to claim 9, wherein said active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

11. The bead according to claim 10, wherein the fraction of active ingredient that is released in vitro is not more than about 30% after 1 hour, from about 40 to about 85% after 3 hours, and not less than about 80% after 7 hours.

12. The bead according to any one of claims 1 to 11, wherein the polymer material of said first layer comprises ethyl cellulose.

13. The bead according to any one of claims 1 to 12, wherein said second layer comprises hydroxypropylmethyl cellulose as binder.

14. The bead according to any one of claims 1 to 13, wherein the polymer material of said third layer comprises a combination of hydroxypropylmethyl cellulose and ethyl cellulose.

15. The bead according to any one of claims 1 to 14, wherein the core unit has a size of about 0.05 to about 2 mm.

16. A multiple unit formulation comprising a controlled release bead according to any one of claims 1 to 15.

17. The multiple unit formulation according to claim 16 which is a capsule.

18. A method of producing a controlled release bead, which method comprises the steps of:

a) providing a core unit of a substantially water-soluble or water-swellable materia;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first is selected to provide a layer thickness that permits control of water penetration into the core.

19. A method for treating overactive bladder, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

20. The method according to claim 19, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

21. A method for treating nocturia, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

22. The method according to claim 21, wherein the active ingredient is tolterodine or a pharmacologically acceptable salt thereof.

23. A method for treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of beads according to any one of claims 8 to 15.

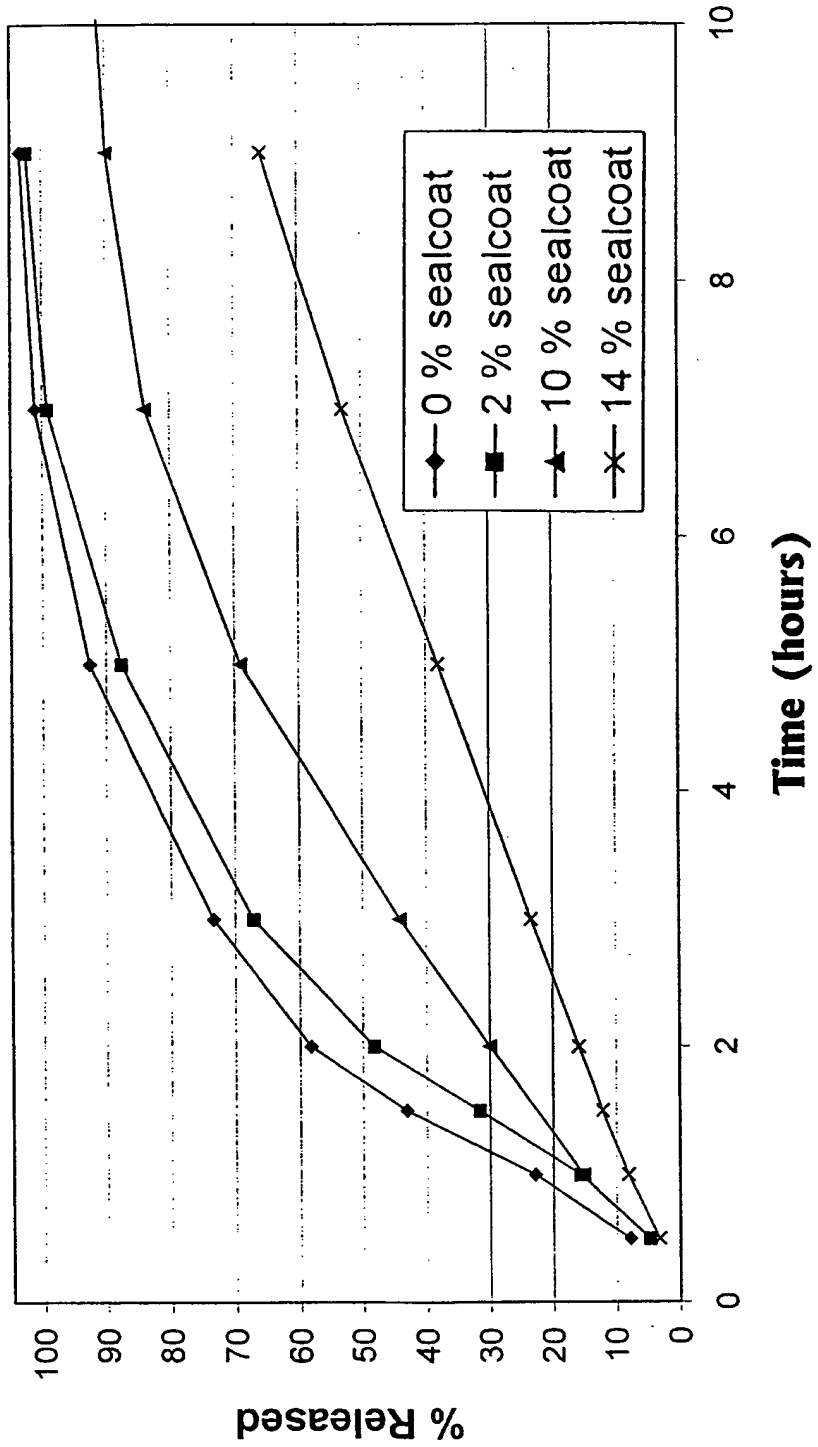


FIG. 1

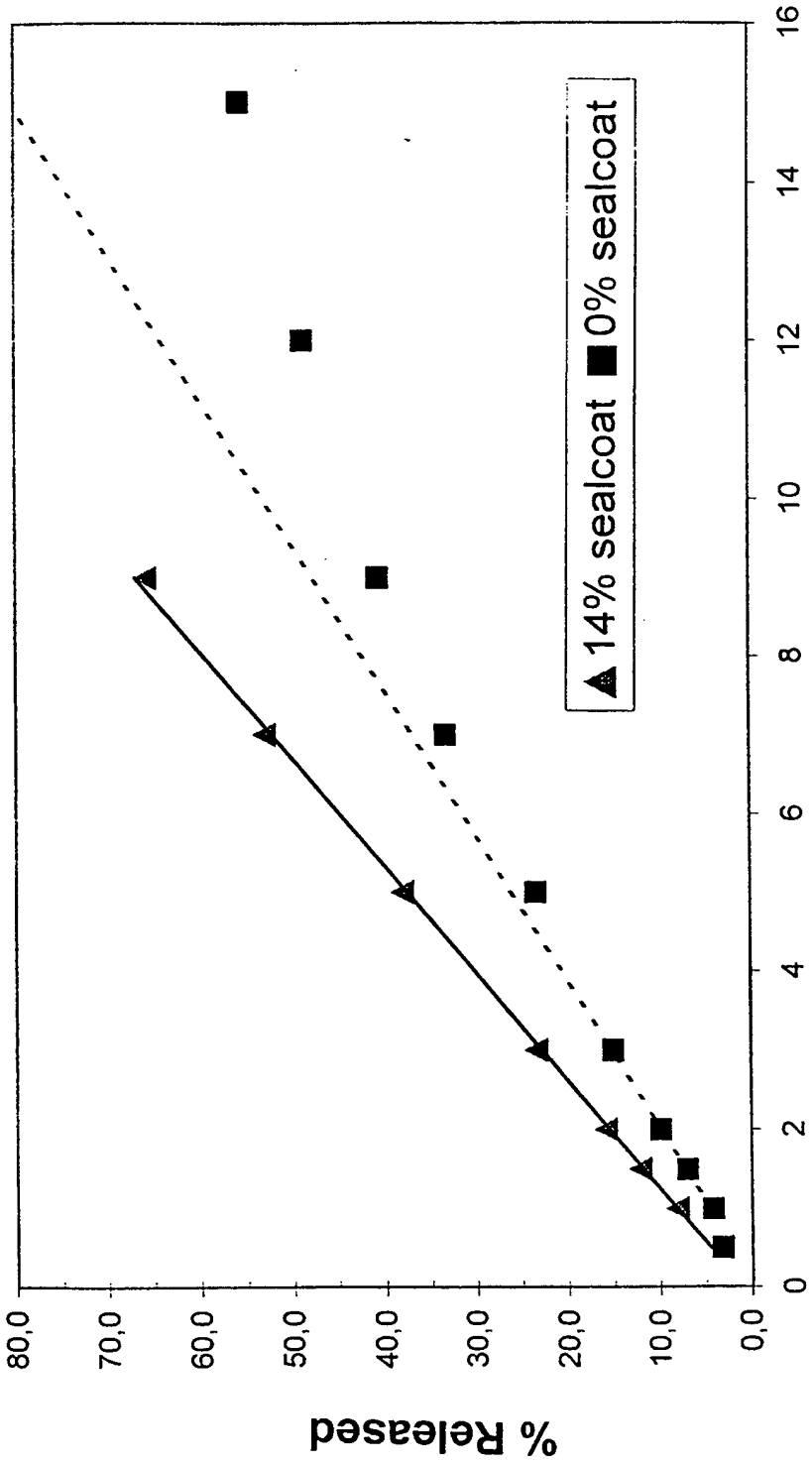


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02052

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/16, A61K 9/26, A61K 9/58, A61K 31/135, A61P 13/10, A61P 1/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9601621 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96) --	1-23
A	WO 9629992 A1 (ANDRX PHARMACEUTICALS, INC.), 3 October 1996 (03.10.96) --	1-23
A	EP 0061217 A2 (PHARMATEC S.P.A.), 29 Sept 1982 (29.09.82) -- --------	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2000	25 -02- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02052

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-23
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02052

Claims 19-23 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 99/02052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601621 A1	25/01/96	AU 700949 B	14/01/99
		AU 2993695 A	09/02/96
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		FI 961056 A	06/05/96
		HU 75772 A	28/05/97
		HU 9600575 D	00/00/00
		IL 114448 D	00/00/00
		JP 9502738 T	18/03/97
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		NZ 289947 A	28/07/98
		PL 313386 A	24/06/96
		SE 9402422 D	00/00/00
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		NZ 305594 A	23/12/98
		US 5567441 A	22/10/96
		US 5834023 A	10/11/98
EP 0061217 A2	29/09/82	DK 121382 A	20/09/82
		IT 1144911 B	29/10/86
		IT 8120578 D	00/00/00

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PCT

(10) International Publication Number
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(74) Agents: **TANNERFELDT, Agneta** et al.; Pharmacia AB, S-112 87 Stockholm (SE).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL FORMULATION CONTAINING TOLTERODINE AND ITS USE

(57) Abstract: The invention relates to a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders.

WO 01/34139 A1

Pharmaceutical formulation containing tolterodine and its use.

The present invention relates to a pharmaceutical formulation for administering tolterodine or a tolterodine-related compound, and to the medical use of such a formulation.

A substantial part (5-10%) of the adult population suffers from overactive or unstable urinary bladder, often also referred to as urinary incontinence. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly of so-called urge incontinence, increases with age. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Recently, however, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195-207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647-655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287-295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While,

as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

Our co-pending international application PCT/SE99/01463 relates to the administration of tolterodine and tolterodine-related compounds through a controlled release formulation and is based on the finding that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

Our above-mentioned PCT/SE99/01463 discloses treatment of overactive bladder by the administration of a controlled release formulation that delivers tolterodine, a tolterodine-related compound, or a pharmacologically acceptable salt thereof such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

The present invention is based on the unexpected observation that a substantially constant serum level of the active moiety or moieties for 24 hours may be obtained through oral administration of a controlled release pharmaceutical formulation that releases the major content of active compound in less than about 18 hours, and more particularly that the formulation has an in vitro release of not less than about 80 % after 18 hours at the conditions specified below.

In one aspect, the present invention therefore provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation

exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

A second aspect of the invention relates to the use of the pharmaceutical formulation for treating a disorder or disease selected from overactive bladder (including i.a. urinary incontinence and nocturia) and gastrointestinal disorders.

A third aspect of the invention relates to the use of tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, for the preparation of the pharmaceutical formulation of the above first aspect of the invention.

Preferably, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released is not less than about 80 % after 15 hours, especially not less than about 80 % after 12 hours.

On the other hand, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after 1 hour is preferably not more than about 50 %, especially not more than about 30%.

The fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after three hours is preferably from about 30 to 95 %, especially from about 40 to about 85 %.

It may be preferred that after 7 hours, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 50 %, especially not less than about 80 %.

In an exemplary in vitro release profile for the pharmacutical formulation, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50 % after 1 hour, from about 30 to about 95 % after 3 hours, and more than about 50 % after 7 hours.

The in vitro release measurement conditions referred to above are those for a drug release test that utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37°C, where the phosphate buffer solution is prepared as described on pages 2049-2050 in USP 23. The phosphate buffer nominally contains 0.05 M phosphate.

By the term "active moiety or moities" it is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any substantial peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI = (Cmax - Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

The formulation of the present invention is not restricted to any particular type of formulation. Thus, various types of controlled or sustained release type formulations may be used for embodying the present invention, such as, for example, osmotic tablets, gel matrix tablets, coated beads, etc.

A common type of controlled release formulation that may be used for the purposes of the present invention comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" may be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat is preferably in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead may thus comprise:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein the first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-

thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60 % (w/w), preferably from about 0.1 to about 30 % (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50 % (w/w), preferably from about 2 to about 25 % (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

The controlled release beads may be provided in a multiple unit formulation, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores may be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

The above controlled release beads and formulation, respectively may be produced by a method comprising the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient;

wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, one or more additional polymer layers are applied to the core as has been mentioned above.

The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30-80°C, for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35°C before stopping the process.

As mentioned above, the pharmaceutical formulation according to the present invention may be used for treating, *inter alia*, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The formulation may also be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

The pharmaceutical formulation according to the present invention has proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urinary incontinence (urge incontinence), urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned US-A-5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned US-A-5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

Fig. 1 is a diagram showing the fraction of tolterodine L-tartrate released in vitro versus time for 2 and 4 mg controlled release capsules according to the Example below; and

Fig. 2 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through a prolonged release (PR) capsule (4 mg) according to the Example below once daily. The corresponding variation with a prior art immediate release (IR) tablet (2 mg) twice daily is also shown.

EXAMPLE

Preparation of controlled release beads and capsules

An exemplary bead formulation containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73 % w/w of the final bead; purpose: coating substrate;
First layer:	Surelease® "sealcoat" (Surelease® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12 % w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;
Second layer:	Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3 % w/w of the final bead; ratio of Tolterodine:HPMC is 5:1; purpose: drug supply;
Third layer:	Surelease®/HPMC; comprises about 12 % w/w of the final bead; ratio of Surelease®:HPMC is 6:1; purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20-25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40°C with the following three coating liquids:

- (1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
- (2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
- (3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70°C, the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20-25 mesh	68.6 mg	137.2 mg
Surelease®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer: HPMC; comprises about 1 % w/w of the final bead;
purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Drug in vitro release study

A drug-release test which utilizes the USP Apparatus 1 (rotating basket) at 100 rpm with 1000 mL of deaerated phosphate buffer prepared at pH 6.8, was used to study the in vitro release at 37°C of the two three-layered beads-containing 2 and 4 mg capsules prepared above. The buffer was identical to that used for the Buffer Stage testing of Delayed-release dosage forms described in USP 23 General Chapter 724, and nominally contains 0.05 M phosphate and 0.075 M chloride. The results are shown in Fig. 1. As can be seen therein, about 90 % of the tolterodine tartrate had been released from both capsules after 12 hours.

Pharmacokinetic study – Determination of serum concentrations of tolterodine and main metabolite

A clinical trial was performed in patients with overactive bladder to determine the pharmacokinetic effects of a (i) a once daily dose of a 4 mg tolterodine controlled release capsule (below referred to as TOD) as described above, and (ii) two doses daily of a tolterodine immediate release tablet (below referred to as TIR), described below. 30 patients were subjected to each of the treatments. The measurements were performed on day seven in each treatment period and included measurements of serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136). Figure 2 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily (PR capsule in Fig. 2), and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus

providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI = (Cmax - Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.29 (95% CI 1.95-2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59-0.78) for the TOD capsule.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow. Thus, for example, other sustained release formulations may be used.

CLAIMS

1. A pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, which formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

2. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80 % after 15 hours.

3. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80 % after 12 hours.

4. The formulation according to claim 1, 2 or 3, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50 % after 1 hour.

5. The formulation according to claim 4, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 30 % after 1 hour.

6. The formulation according to claim any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 30 to about 95 % after 3 hours.

7. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 40 to about 85 % after 3 hours.

8. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 50 % after 7 hours.

9. The formulation according to any one of the preceding claims, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 80 % after 7 hours.

10. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not more than about 50 % after 1 hour, from about 30 to about 95 % after 3 hours, and not less than about 50 % after 7 hours.

11. The formulation according to any one of the preceding claims, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37 °C, where the phosphate buffer solution is prepared as described on pages 2049-2050 of USP 23, and nominally contains 0.05 M phosphate.

12. The formulation according to any one of the preceding claims, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, preferably not higher than about 1.0, said flutuation index, FI, being defined as $FI = (Cmax - Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

13. The formulation according to any one of the preceding claims, which comprises tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a salt thereof.

14. The formulation according to any one of the preceding claims, which comprises tolterodine, or a salt thereof.

15. The formulation according to claim 14 or 15, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 5 to about 150 nM*h, preferably from about 10 nM*h to about 120 nM*h.

16. The formulation according to claim 14 or 15, wherein and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

17. A method for treating overactive bladder, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

18. A method for treating urinary incontinence, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

19. A method for treating nocturia, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

20. A method for treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 16.

21. Use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for

treating a disorder selected from overactive urinary bladder, including urinary incontinence, nocturia and gastrointestinal disorders, which formulation exhibits a controlled in vitro release of tolterodine, a tolterodine-related compound or pharmacologically acceptable salt thereof, in phosphate buffer at pH 6.8 of not less than about 80 % after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

22. A method for orally administering tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, to a patient to maintain a substantially constant serum level of the active moiety or moieties for 24 hours, which method comprises administering a pharmaceutical formulation containing tolterodine, a tolterodine-related compound or a salt thereof, which formulation exhibits a controlled in vitro release in phosphate buffer at pH 6.8 of tolterodine, tolterodine-related compound or salt thereof of not less than about 80 % after 18 hours.

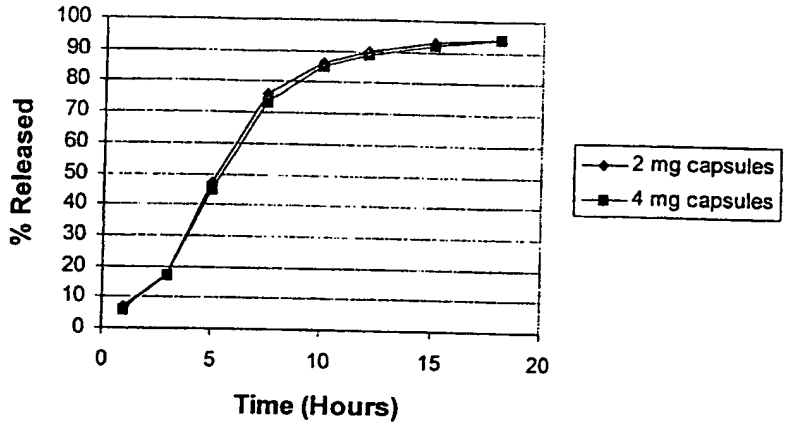
100
90
80
70
60
50
40
30
20
10
0
% Released
0
5
10
15
20
Time (Hours)
2 mg capsules
4 mg capsules

FIG. 1

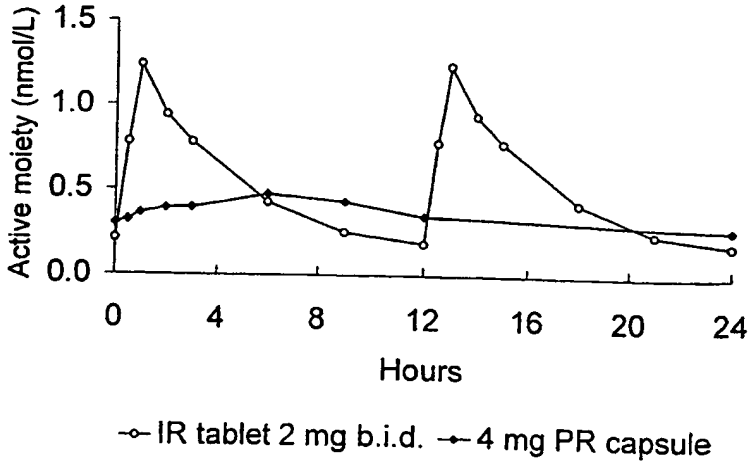
1.5
1.0
0.5
0.0
Active moiety (nmol/L)
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02061

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/135, A61K 9/16, A61K 9/26, A61P 13/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0012069 A1 (PHARMACIA & UPJOHN AB), 9 March 2000 (09.03.00), see page 7, lines 22-30 --	1-22
P,X	WO 0027364 A1 (PHARMACIA & UPJOHN AB), 18 May 2000 (18.05.00) --	1-22
A	WO 9803067 A1 (ABERG, GUNNAR), 29 January 1998 (29.01.98) -- --------	1-22

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2001	29 -03- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02061

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-20, 22
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02061

Claims 17-20, 22 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0012069 A1	09/03/00	AP 200001823 D	00/00/00
		AU 5891899 A	21/03/00
		AU 5891999 A	21/03/00
		EP 1039882 A	04/10/00
		NO 20002977 A	09/06/00
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		WO 0012070 A	09/03/00
		AU 1436600 A	29/05/00
		SE 9803871 D	00/00/00
		WO 0027364 A	18/05/00
WO 0027364 A1	18/05/00	AP 200001823 D	00/00/00
		AU 1436600 A	29/05/00
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		JP 2000515525 T	21/11/00

DFW

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT		Docket Number: **12961/46102**	
Application Number **10/766,263**	Filing date **January 27, 2004**	Examiner **Z.C. TUCKER**	Art Unit **1624**
Invention Title **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s) **MEESE, et al.**	

Address to:

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on: February 14, 2006

By: Joseph A Coppola
Joseph A. Coppola (Reg. No. 38,413)

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 37 C.F.R. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorneys for Applicant hereby brings the attached references to the attention of the Examiner. These references are listed on the attached modified PTO Form No. 1449. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. The filing of this Information Disclosure Statement and the attached PTO Form No. 1449, shall not be construed as an admission that the information cited is prior art, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b).

3. A copy of each patent, publication or other information listed on the modified PTO form 1449 are enclosed unless otherwise noted.

4. It is believed that no fees are due in connection with this Information Disclosure Statement. However, should any fees be due, the Commissioner is authorized to charge or credit any over payment to Deposit Account No. 11-0600. A duplicate copy of this communication is enclosed for charging purposes.

Dated: February 14, 2006

By: Joseph A Coppola
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CUSTOMER NO. 26646

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449	ATTY. DOCKET NO. **12961/46102**	APPLICATION NO. **10/766,263**
	APPLICANT **Z.C. TUCKER**	
	FILING DATE **January 27, 2004**	GROUP **1624**

U. S. PATENT DOCUMENTS*

EXAMINER INITIAL	PATENT/PUBLICATION NUMBER	PATENT/PUBLICATION DATE	NAME	CLASS	SUBCLASS	FILING DATE*
	2003/0152624	August 14, 2003	Aldrich et al.			
	2003/0158176	August 21, 2003	Richards et al.			
	2004/064821	April 1, 2004	Rousselle			
	3,216,841	July 19, 1966	Zenitz			
	6,310,248	October 30, 2001	Andersson et al.			
	6,566,537	May 20, 2003	Andersson et al.			
	6,689,916	February 10, 2004	Andersson et al.			

*- copies of U.S. references are not enclosed

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
	766,207	December 22, 1952	DE			YES	
	831,799	June 7, 1996	EP				
	872,233	April 14, 1997	EP				
	948,321	December 10, 1997	EP				NO
	957,073	May 12, 1998	EP				
	1,025,041	February 24, 1964	GB				
	WO 02/089773	November 14, 2002	PCT				
	WO 02/11702	February 14, 2002	PCT				
	WO 03/002059	January 9, 2003	PCT				
	WO 03/007918	January 30, 2003	PCT				
	WO 03/020241	March 13, 2003	PCT				
	WO 03/026564	April 3, 2003	PCT				
	WO 03/035599	May 1, 2003	PCT				
	WO 03/039464	May 15, 2003	PCT				
	WO 03/063834	August 7, 2003	PCT				
	WO 03/099268	December 4, 2003	PCT				NO
	WO 03/103637	December 18, 2003	PCT				
	WO 03/106421	December 24, 2003	PCT				
	WO 04/019892	March 11, 2004	PCT				
	WO 98/43942	October 8, 1998	PCT				
	WO 98/56359	December 17, 1998	PCT				NO
	WO 99/58478	November 18, 1999	PCT				

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EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Lipinski, et al., "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings" Elsevier Advanced Drug Delivery Reviews Vol. 23, pp. 3-25, 1997
		Netzer, et al., "Screening lead compounds for QT interval prolongation" Drug Discovery Today Vol. 6, No. 2, pp.78-84, January 2001
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		Roy, et al., "HERG, a Primary Human Ventricular Target of the Nonsedating Antihistamine Terfenadine" Circulation Vol. 94, No. 4, pp. 817-823, August 15, 1996

EXAM INER	DATE CONSIDERED
EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

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60/391,521	25 June 2002 (25.06.2002)	US

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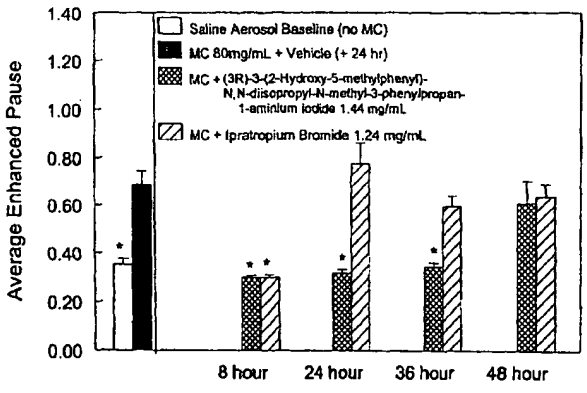
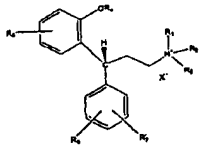
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

[Continued on next page]

(54) Title: QUARTERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS



* : p < 0.05 between Vehicle/MC and all other groups



(I)

(57) Abstract: Novel quaternary ammonium compounds of the formula (I) and any stereoisomers thereof, wherein, R_1, R_2, and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen; R_4 represents -H, $-CH_3$, or -CO-R_{4-1}, wherein R_{4-1} represents -(C_1-C_4 alkyl), -(C_1-C_4 alkoxy), or $NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl); R_5, R_6 and R_7 independently represent -H, $-OCH_3$, -OH, $-CONH_2$, $-SO_2NH_2$, -F, -Cl, -Br, -I, $-CF_3$, or -(C_1-C_4 alkyl), optionally substituted with one or two -OH, -(C_1-C_4 alkoxy), -COOH, or -CO-O-(C_1-C_3 alkyl); and X represents an anion of a pharmaceutically acceptable acid, the compounds for use as medicaments, use of the compounds for the manufacture of specific medicaments, and pharmaceutical compositions comprising the compounds. The present invention also concerns a method of treatment involving administration of the compounds.

WO 03/035599 A1

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

QUATERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS

This application claims the benefit of US Provisional Patent Application No. 60/348 930, filed 26 October 2001, US Provisional Patent Application No. 60/361 979, filed 6 March 2002, and US Provisional Patent Application No. 60/391 521, filed 25 June 2002, and the entire disclosures of which are herein incorporated by reference.

Technical Field

The present invention concerns a novel class of quaternary ammonium compounds, pharmaceutical compositions containing the same, the compounds for use as medicaments, and use of the compounds for the manufacture of specific medicaments. The present invention also concerns a method of treatment involving administration of the compounds.

The novel compounds are useful as antimuscarinic agents. In particular, the novel compounds are useful for the treatment of asthma, a group of breathing disorders termed Chronic Obstructive Pulmonary Disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

Background of the Invention

US Patent 5,382,600 discloses (substituted) 3,3-diphenylpropylamines useful for treating urinary incontinence. In particular, it discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl)-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as being useful to treat urinary incontinence. Tolterodine is the compound of Example 22 of US 5,382,600.

It is preferred that tolterodine is prepared by the processes of International Publication WO98/29402 (US 5,922,914).

H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major, active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine.

US Patent 5,559,269 and H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity.

The international patent application WO98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related to urinary incontinence.

WO 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg or 2 mg of tolterodine L-tartrate, or extended release capsules containing 2 mg or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms with favorable efficacy and/or which simplify the treatment, thus improving their quality of life.

Atropine methonitrate and ipratropium are quaternary ammonium derivatives of atropine. Ipratropium bromide is

used by inhalation to produce bronchodilation. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

Yono M *et al*, European Journal of Pharmacology (1999) 368:223-230, is concerned with the pharmacological effects of tolterodine, an antimuscarinic drug, in isolated human urinary bladder smooth muscle.

Ruffmann R *et al*, The Journal of International Medical Research (1998) 16:317-330, reviews use of flavoxate hydrochloride or alternative compounds, such as terodiline hydrochloride and emepronium bromide, in the treatment of urge incontinence.

Stewart BH *et al*, The Journal of Urology (1976) 115:558-559 discloses therapy of mild to moderate stress urinary incontinence with a combination of phenylpropanolamine hydrochloride, chlorpheniramine maleate, and isopropamide iodide in a sustained release capsule.

WO 95/10269 and WO 95/10270 disclose the use of R- and S-terodiline, respectively, as drugs for treating conditions related to the compounds' activities as anticholinergic agents.

Despite the above advances in the art, it is desirable to develop novel pharmaceutical compounds that further improve the quality of life for a large number of individuals.

Summary of the Invention

For these and other purposes, it is an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of asthma.

It is also an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of Chronic Obstructive Pulmonary Disease (COPD).

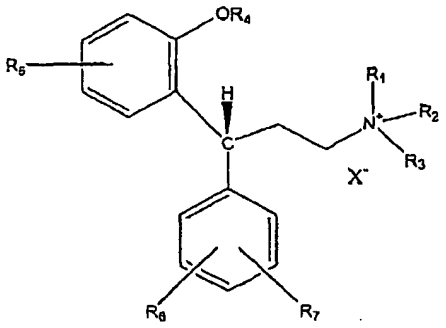
It is a further object of the present invention to provide highly efficient pharmaceutical compounds for treatment of allergic rhinitis.

It is an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of rhinorrhea due to the common cold.

It is also an object of the present invention to provide pharmaceutically effective 3,3-diphenylpropylamine derivatives having an increased residence time in lung upon pulmonary administration.

It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamine derivatives having favorable properties.

For these and other objects that will be evident from the following disclosure, the present invention provides a quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 represents

-H,

-CH_3, or

-CO-R_{4-1} wherein R_{4-1} represents

-(C_1-C_4 alkyl),

-(C_1-C_4 alkoxy), or

$-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl), and

R_5, R_6 and R_7 independently represent

-H,

$-OCH_3$,

-OH,

$-CONH_2$,

$-SO_2NH_2$,

-F, -Cl, -Br, -I,

$-CF_3$, or

-(C_1-C_4 alkyl), optionally substituted with one or two

-OH,

-(C_1-C_4 alkoxy),

-COOH, or

-CO-O-(C_1-C_3 alkyl), and

X^- represents an anion of a pharmaceutically acceptable acid.

In an embodiment of the compound according to the invention, the carbon stereocenter is (R). In another embodiment of the compound according to the invention, the carbon stereocenter is (S). In yet another embodiment, the compound according to the invention is a mixture of stereoisomers.

In a preferred embodiment of the compound according to the invention, at least one of R_1, R_2 and R_3 represents C_1-C_3 alkyl. In a more preferred embodiment, at least one, preferably at least two, of R_1, R_2 and R_3 represents isopropyl. In another more preferred embodiment, at least one of R_1, R_2 and R_3 represents methyl. In yet another more preferred embodiment, at least one of R_1, R_2 and R_3 represents ethyl.

In one preferred embodiment of the compound according to the invention, R_1 and R_2 jointly form a ring together with the quaternary ammonium nitrogen. In a more

preferred embodiment, said ring comprises from 4 to 6 carbon atoms.

In a preferred embodiment of the compound according to the invention, R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents C_1-C_4 alkyl. In a more preferred embodiment, R_4 represents -H.

In a preferred embodiment of the compound according to the invention, R_5 represents -H, -Br, -Cl, $-CH_3$, or $-CH_2OH$, more preferably $-CH_3$.

In a preferred embodiment of the compound according to the invention, at least one, more preferably both, of R_6 and R_7 represents -H.

In a preferred embodiment of the compound according to the invention, X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)n-COOH$ where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic. In a more preferred embodiment, X^- is selected from the group consisting of iodide, bromide, and chloride. In an even more preferred embodiment, X^- represents iodide. In another even more preferred embodiment, X^- represents chloride. In yet another even more preferred embodiment, X^- represents bromide.

More specifically, preferred embodiments of the compound according to the invention include the title compounds of the examples. Particularly preferred embodiments are selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide, and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

Moreover, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a quaternary ammonium compound according to the invention, and a suitable pharmaceutical carrier therefor.

The present invention also provides a quaternary ammonium compound according to the invention for use as a medicament.

The present invention provides use of a quaternary ammonium compound according to the invention for the manufacture of a medicament for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder.

Finally, the present invention provides a method of treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to the invention.

Brief Description of the Drawings

Figures 1-3 are diagrams showing average enhanced pause (lung resistance) as a function of time upon inhalation of quaternary ammonium salts according to the invention in Balb/c mice.

Figure 4 is a diagram showing the effects of inhalation of tolterodine and a compound according to the invention, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 5 is a diagram showing the effects of inhalation of a compound according to the invention and ipratropium bromide, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 6 is a diagram showing the plasma concentration (pg/ml) of a compound according to the invention with time (hours) following aerosol administration of various amounts in Balb/c mice.

Figure 7 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) following aerosol administration of various amounts in mice.

Description of the Invention

In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments, as well as all technical equivalents that operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo, and, is expressly intended to include all enantiomers, isomers or tautomers where the compound is capable of being present in its enantiomeric, isomeric or tautomeric form.

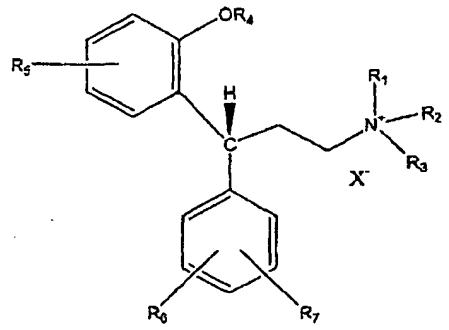
The compounds of the invention can be prepared by one skilled in the art just by knowing the chemical structure of the compound to be prepared. The invention is the compounds themselves, not the process chemistry to make them. The chemistry is known to those skilled in the art.

Accordingly, the compounds of the present invention are quaternary ammonium compounds and are prepared by means, well known to those skilled in the art, for preparing quaternary ammonium compounds from tertiary amines, using the tertiary amines of US Patent 5,382,600 and other known compounds as starting materials. The general term "quaternary ammonium compound" relates to

any compound that can be regarded as derived from ammonium hydroxide or an ammonium salt by replacement of all four hydrogen atoms of the NH_4^+-ion by organic groups.

The specific compounds are for nomenclature reasons (see e.g. Chemical Abstracts) named as "aminium" compounds, but it is possible to use the term "ammonium" in the names. For example, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide can also be named as an ammonium compound: (3R)-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]diisopropylmethylammonium bromide.

More specifically, the invention concerns quaternary ammonium compounds of the formula:



and any stereoisomers thereof, wherein R_1-R_7 and X^- are as follows.

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen.

R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents -(C_1-C_4 alkyl), -(C_1-C_4 alkoxy), or $-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or -(C_1-C_4 alkyl).

R_5, R_6 and R_7 independently represent -H, $-OCH_3$, -OH, $-CONH_2$ (carbamoyl), $-SO_2NH_2$ (sulphamoyl), -F, -Cl, -Br, -I, $-CF_3$, or -(C_1-C_4 alkyl), optionally substituted with

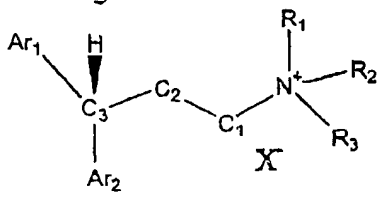
one or two -OH, -(C_1-C_4 alkoxy), -COOH, or -CO-O-(C_1-C_3 alkyl), and X^- represents an anion of a pharmaceutically acceptable acid.

By way of example, a tertiary amine according to US Patent 5,382,600, or its salt, is dissolved in a suitable solvent. The tertiary amine is allowed to react with an organic substrate, e.g. an organic halide.

The substrate contains a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl, optionally substituted with phenyl, and a leaving group. The identity of the leaving group is not critical, but it is preferred that the leaving group is a halide, such as iodide or bromide. Thus, exemplary substrates include methyl iodide, methyl bromide, ethyl iodide, propyl iodide, benzyl bromide or benzyl iodide.

The resulting reaction product is a quaternary ammonium compound, which is readily crystallized in suitable solvents, known to those skilled in the art. The crystals thus produced are quaternary ammonium salts. Their identity is confirmed by standard methods, such as melting point determination, nuclear magnetic resonance (NMR) analysis and mass spectrometry.

The quaternary ammonium compounds of the invention have at least one stereocenter, i.e. the carbon in position 3 (C_3 in the formula below), to which two (substituted) aryl groups are attached. Optionally, there may be a second stereocenter (when R_1, R_2 and R_3 all are different), the positively charged quaternary ammonium nitrogen atom. See the general formula:



wherein Ar_1 and Ar_2 denote (substituted) aryl groups, R_1, R_2, R_3 and X^- are as above, and C_1, C_2 and C_3 denote individual carbon atoms in the propylammonium backbone. Accordingly, stereoisomers (enantiomers and/or diastereomers) are produced. All stereoisomers have useful activity. Therefore, the invention includes use of each stereoisomer separately, as well as mixtures thereof. Specifically, the stereoisomers in which the C_3 carbon stereocenter is in the (R) form have useful activity. Moreover, the stereoisomers in which the C_3 carbon stereocenter is in the (S) form have useful activity. A mixture of stereoisomers, comprising the stereoisomers in which the C_3 carbon stereocenter is in the (R) form and the stereoisomers in which the C_3 carbon stereocenter is in the (S) form, also has useful activity.

The quaternary ammonium compounds of the invention are preferably administered as salts with a pharmaceutically acceptable acid. Where R_4 is -H, the compounds can be isolated as internal salts, which have a phenoxide anion to balance the positive charge on the quaternized nitrogen. The preferred pharmaceutically acceptable salts include salts of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, CH_3-$(CH_2)_n$-COOH where n is 0 thru 4, HOOC-$(CH_2)_n$-COOH where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic. For other acceptable salts, see Int. J. Pharm., 33, 201-217 (1986). Particularly preferred salts are chloride, iodide and bromide salts, especially bromide salts and iodide salts.

Accordingly, X^- represents an anion of a pharmaceutically acceptable acid. Preferably, X^- is selected from the following anions: tartrate, chloride, bromide, iodide, sulfate, phosphate(s), nitrate, citrate, methanesulfonate, carboxylates with from two to six

carbon atoms, dicarboxylates with from two to six carbon atoms, maleate, fumarate, and benzoate. It is preferred that X^- represents chloride, iodide or bromide, more preferred iodide or bromide.

The substituents R_1, R_2, R_3 may be the same or different. They are selected from the group comprising C_1-C_6 alkyls, preferably C_1-C_5 alkyls, straight or branched, optionally substituted with phenyl or hydroxyl, or both. Thus, R_1, R_2, R_3 independently represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, or isohexyl, optionally substituted with phenyl or hydroxyl, or both.

It is preferred that at least one of the substituents R_1, R_2, R_3 represents a C_1-C_3 alkyl, straight or branched, i.e. methyl, ethyl, propyl, or isopropyl. It is particularly preferred that one of the substituents R_1, R_2, R_3 represents methyl or ethyl, preferably methyl. It is also preferred that at least one, more preferred two, of the substituents R_1, R_2, R_3 represent(s) isopropyl. It is especially preferred that R_1 and R_2 each represent isopropyl, and R_3 represents methyl or ethyl, preferably methyl. The substituents R_1, R_2, and R_3 together contain at least 3 carbon atoms. It is preferred that the substituents R_1, R_2, and R_3 together contain at least 4 carbon atoms, more preferred at least 5 carbon atoms, even more preferred at least 6 carbon atoms.

According to another aspect of the invention, any two of R_1, R_2, and R_3 may jointly form a ring structure together with the positively charged nitrogen. It is preferred that the resulting ring structure comprises from four to six carbon atoms.

The substituent R_4 is attached via an oxygen atom to its aryl ring. The $-OR_4$ group is attached to the carbon atom in position 2 in the ring, with respect to the

propylammonium group. The substituent R_4 may represent hydrogen, methyl or acyl (-CO-R_{4-1}), wherein acyl includes any one of the following: alkylcarbonyl, straight or branched, having from two to five carbon atoms, alkoxycarbonyl, straight or branched, having from two to five carbon atoms, and amide, optionally mono- or independently disubstituted with alkyl, straight or branched, having from one to four carbon atom(s). Accordingly, the substituent R_{4-1} represents any one of the following: C_1-C_4 alkyl, straight or branched, C_1-C_4 alkoxy, straight or branched, and -$NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} may be the same or different and represent -H or -(C_2-C_4 alkyl), straight or branched. Thus, the substituent R_4 may represent any one of the following: hydrogen, methyl or acyl, wherein the acyl group may be acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl, or an N,N-dialkylcarbamoyl, wherein the alkyl groups, straight or branched, are the same or different and have from 1 to 4 carbon atoms each. Examples of N,N-dialkylcarbamoyls in this position include N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, as well as N,N-diisobutylcarbamoyl, and N-propyl-N-butylcarbamoyl. It is preferred that R_4 represents hydrogen, since such compounds can be isolated as internal salts, which have a phenoxide anion to balance the positive charge on the quaternized nitrogen. It is also preferred that R_4 represents alkylcarbonyl, straight or branched, having from two to five carbon atoms, e.g. acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, or isopentanoyl. Moreover, it is preferred that R_4 represents methyl.

The substituent R_5 may be connected to any, otherwise not substituted, carbon atom in its aryl ring. In other words, R_5 is not connected to any of the carbon atoms to which the $-OR_4$ group or the (substituted) phenylpropanammonium group is connected, but R_5 may be connected to any one of the remaining four carbon atoms in its aryl ring.

R_5 may represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl ($-CO-O-(C_1-C_3$ alkyl)), straight or branched, having from one to four carbon atoms. It is preferred that R_5 represents any one of the following: hydrogen, bromine, chlorine, methyl or hydroxymethyl. It is particularly preferred that R_5 represents methyl. If R_5 does not represent hydrogen, it is preferred that R_5 is situated opposite the $-OR_4$ group, i.e. at the carbon atom in position 5 in the ring, with respect to the propylammonium group.

The substituents R_6 and R_7 are connected to the same aryl ring, which is different from the aryl ring to which the substituents R_4 and R_5 are connected. R_6 and R_7 may be the same or different. R_6 and R_7 may independently represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl

(-CO-O-(C_1-C_3 alkyl)), straight or branched, having from one to four carbon atoms.

It is preferred that at least one, preferably both, of R_6 and R_7 represents hydrogen. When one, but not both, of R_6 and R_7 represents hydrogen, it is preferred that the other (R_7 or R_6, respectively) is attached to the carbon atom in position 2 in the ring, with respect to the propylammonium group. When neither R_6 nor R_7 represent hydrogen, it is preferred that one is attached to the carbon atom in position 2 and the other to any one of the carbon atoms in positions 3, 4, or 5, respectively, in the ring, with respect to the propylammonium group.

The novel class of compounds according to the present invention are antimuscarinic agents. "Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of known antimuscarinic agents include tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, ipratropium, and tiotropium.

Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha,alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha. cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-

isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337. Tiotropium is (1-alpha,2-beta,4-beta,5-alpha,7-beta)-7-[(hydroxydi-(2-thienyl)acetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane and is disclosed in EP 418,716.

The compounds of the invention have anti-cholinergic properties. Thus, they are useful for the treatment of acetylcholine-mediated disorders. In particular, they are useful for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

"Asthma" refers to a chronic lung disease causing bronchoconstriction (narrowing of the airways) due to inflammation (swelling) and tightening of the muscles around the airways. The inflammation also causes an increase in mucus production, which causes coughing that may continue for extended periods. Asthma is characterized by recurrent episodes of breathlessness, wheezing, coughing, and chest tightness, termed exacerbations. The severity of exacerbations can range from mild to life threatening. The exacerbations can be a result of exposure to e.g. respiratory infections, dust, mold, pollen, cold air, exercise, stress, tobacco smoke, and air pollutants.

"COPD" refers to Chronic Obstructive Pulmonary Disease, primarily associated with past and present cigarette smoking. It involves airflow obstruction, mainly associated with emphysema and chronic bronchitis. Emphysema causes irreversible lung damage by weakening and breaking the air sacs within the lungs. Chronic Bronchitis is an inflammatory disease, which increases mucus in the airways and bacterial infections in the bronchial tubes,resulting in obstructed airflow.

"Allergic rhinitis" refers to acute rhinitis or nasal rhinitis, including hay fever. It is caused by

allergens such as pollen or dust. It may produce sneezing, congestion, runny nose, and itchiness in the nose, throat, eyes, and ears.

"Rhinorrhea due to the common cold" refers to watery discharge from the nose in association with a virus infection, such as the common cold. The rhinorrhea may be caused by rhinitis due to a virus infection (such as the common cold).

"Urinary disorders" and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

Overactive urinary bladder encompasses variants of urinary disorders, including overactive detrusor (detrusor instability, detrusor hyperreflexia) and sensory urgency, as well as symptoms of detrusor overactivity, e.g. urge incontinence, urgency, urinary frequency, and LUTS (Lower Urinary Tract Symptoms), including obstructive urinary symptoms, such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain to urinate at an acceptable rate, or irritating symptoms such as frequency, dry overactive bladder, and/or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia), including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet

obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

The compounds of the present invention are used to treat mammals, including man and horse. It is preferred that the mammal is a human.

The compounds according to the invention, in the form of free base or salts with pharmaceutically acceptable acids, or solutions thereof, can be brought into suitable dosage forms, such as compositions for administration through the oral, rectal, transdermal, parenteral, nasal, or pulmonary route in accordance with accepted pharmaceutical procedures. In particular, the compositions may be administered via inhalation or insufflation. Such pharmaceutical compositions according to the invention comprise the compounds according to the invention in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, binders, disintegrants, lubricants, glidants, antiadherents, propellants, and the like.

The novel compounds according to the present invention can be administered in any suitable way. The compounds according to the invention can be made up in

solid or liquid form, such as tablets, capsules, powders, syrups, elixirs and the like, aerosols, sterile solutions, suspensions or emulsions, and the like. They are advantageously administered via inhalation or insufflation. When the administration form is inhalation or insufflation, the compounds are preferably in the form of either an aerosol or a powder.

The term "effective amount" refers to a therapeutically effective amount for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder. The terms "therapy" and "therapeutically" encompass all kinds of treatments, including prophylaxis. In particular, "therapeutically effective" means that it is effective for anti-cholinergic treatment.

The dosage of the specific compound according to the invention will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated.

Doses administrated by inhaler, such as a dry powder inhaler (DPI) or a metered-dose inhaler (MDI), are preferably given as one or two puffs, preferably comprising the total daily dose. For a human subject, it is preferred that the dosage is in the range of from 1 microgram (1 μg) to one milligram (1 mg).

Doses administrated by nebulizer solution are generally higher than doses administrated by inhaler. For a human subject, it is preferred that the total dosage given by nebulizer solution is in the range of from 1 microgram (1 μg) to ten milligrams (10 mg).

Thus, a clinically effective amount of the compounds according to the invention is from about 1 μg to about 10 mg. It is preferred that the effective amount is from about 1 μg to about 1 mg, preferably from about 0.01 mg to about 1 mg.

The compounds of the invention can be administered from one to four times daily. It is preferable to administer the compounds once or twice daily, more preferable once daily.

The dosage form for inhalation can be an aerosol. The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the compounds according to the invention may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many aerosols for treating asthma.

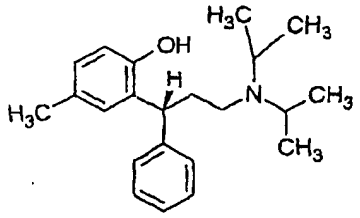
Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When the dosage form is a powder, the compounds according to the invention can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the compounds according to the invention are compounded such that the total amount of powder delivered delivers an "effective amount" of the compounds according to the invention. The actual concentration of the active

compound may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the active compound according to the invention.

For treatment of rhinitis, in particular rhinitis due to the common cold, the compounds according to the invention can advantageously be administered in combination with steroids, cromoglycates, and decongestants (alpha agonists). Such combination therapies are useful in the treatment of rhinorrhea due to the common cold.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:

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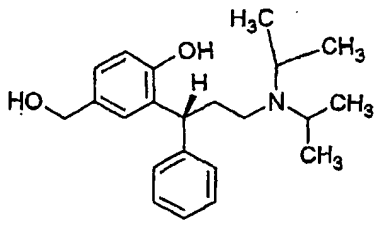


(R)-stereoisomer

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

All temperatures are in degrees Celsius.

Ether refers to diethyl ether.

Physiological saline refers to an 0.9% aqueous sodium chloride solution.

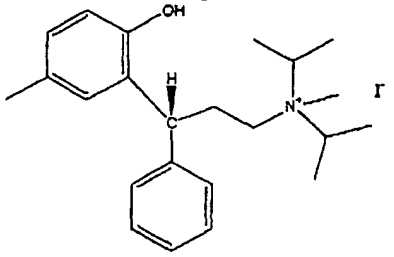
When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

EXAMPLE 1 Tolterodine Free Base

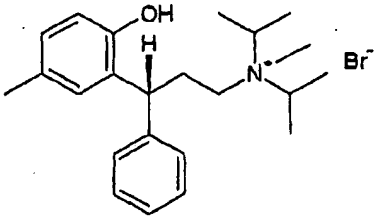
Tolterodine tartrate (2.1 g) is mixed with water (45 ml) and toluene (2.5 ml). Sodium carbonate (800 mg) is added to the slurry. Sodium hydroxide (2.0 N, 1.5 ml) is added. The mixture is extracted three times with toluene (3 ml), saving the organic phase. Anhydrous potassium carbonate is added to the organic phase dissolve the tolterodine tartate, giving the title compound in solution.

EXAMPLE 2 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



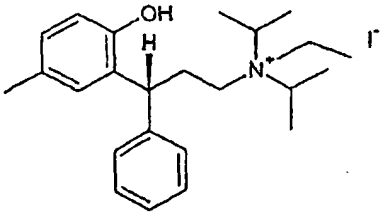
To tolterodine free base (from Example 1, 0.5 M, 2.5 ml) in toluene is added methyl iodide (1 ml). Acetonitrile (5 ml) is added to the mixture and stirred over night at 20-25°C. The solvent is removed by blowing dry nitrogen. Acetone (1 ml) and hexane (2 ml) are added and the mixture is filtered at 20-25°C to give the title compound. Anal Calcd for $C_{23}H_{34}INO$: C, 59.10; H, 7.33; N, 3.00. Found: C, 59.00; H, 7.44; N, 3.00. The identity of the compound has been further verified and characterised by NMR analysis, mass spectrometry, and melting point determination.

EXAMPLE 3 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



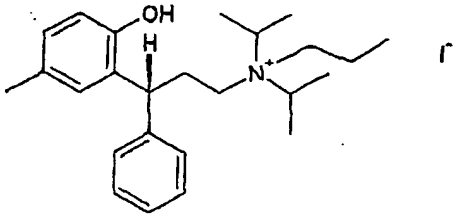
A sealed mixture of methyl bromide (100 g) and 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (14 g) in acetone (100 ml) is stirred at 20-25°C for 4 days. The mixture is cooled to -10°C and the precipitate is filtered off and washed with ether and dried to give the title compound, mp 189-191°C (dec). Anal Calcd for $C_{23}H_{34}BrNO$: C, 65.71; H, 8.15; Br, 19.00; N, 3.33. Found: C, 65.61; H, 8.34; Br, 19.12; N, 3.32. $[\alpha]_D$ (c=1, MeOH) +25°C. ^1H NMR [$(CD_3)_2SO$] δ 1.25, 2.18, 2.48, 2.81, 3.05, 3.89, 4.22, 6.70, 6.83, 7.08, 7.19, 7.33, and 9.3.

EXAMPLE 4 (3R)-N-Ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



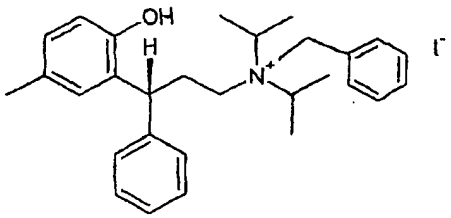
Following the general procedure of Example 2 and making non critical variations, but starting with ethyl iodide, the title compound is obtained.

EXAMPLE 5 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide



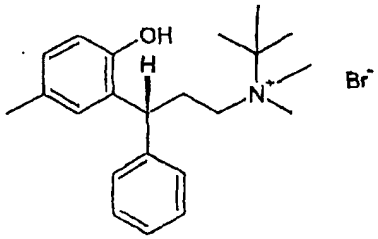
Following the general procedure of Example 2 and making non critical variations, but starting with propyl iodide, the title compound is obtained.

EXAMPLE 6 (3R)-N-Benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with benzyl iodide, the title compound is obtained.

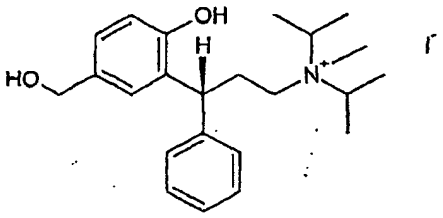
EXAMPLE 7 (3R)-N-(tert-Butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 2 and making non critical variations, but starting with methyl bromide

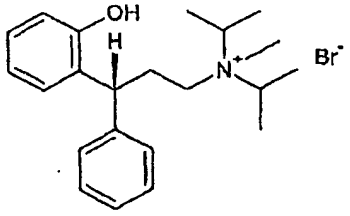
and 2-{(1R)-3-[tert-butyl(methyl)amino]-1-phenylpropyl}-4-methylphenol, the title compound is obtained.

EXAMPLE 8 (3R)-3-[2-Hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



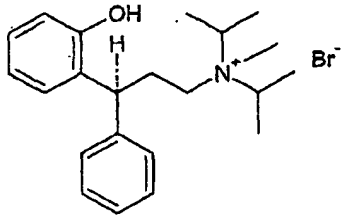
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, the title compound is obtained. Anal Calcd for $C_{23}H_{34}INO_2$: C, 57.14: H, 7.09; N, 2.90. Found: C, 56.33; H, 7.33; N, 2.76. HRMS Calcd 356.2589. Found: 356.2588. ^1H NMR [$(CD_3)_2SO$] δ 1.25, 2.48, 2.81, 3.05, 3.88, 4.26, 4.35, 4.94, 6.75, 6.98, 7.20, 7.33, and 9.5.

EXAMPLE 9 (3R)-3-(2-Hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



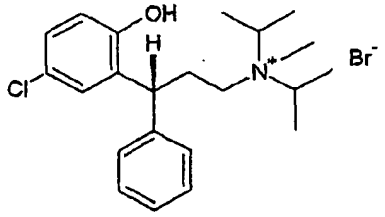
Following the general procedure of Example 3 and making non critical variations but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 10 (3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



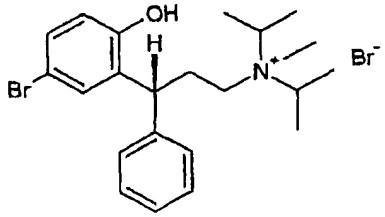
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1S)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 11 (3R)-3-(5-Chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 3 and making non critical variations, but starting with 4-chloro-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

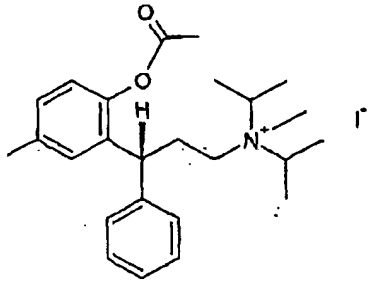
EXAMPLE 12 (3R)-3-(5-Bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 3 and making non critical variations, but starting with 4-

bromo-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 13 (3R)-3-[2-(Acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate

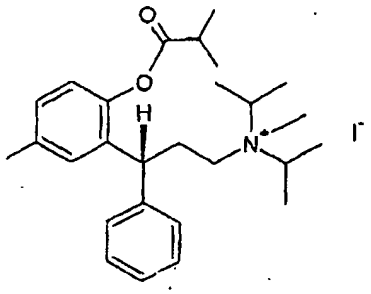
A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (0.9 g) in acetylchloride (20 ml) is stirred at room temperature for 18 h. The acetyl chloride is evaporated, ether is added, and the precipitate of 2-(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate hydrochloride is filtered off; mp 126-130°C. Anal Calcd for $C_{24}H_{33}NO_2 \cdot HCl$: C, 71.35; H, 8.48; Cl, 8.78; N, 3.47. Found: C, 71.02; H, 8.30; Cl, 8.64; N, 3.43. $[\alpha]_D$ (c=1, MeOH) +11°.

The hydrochloride salt is partitioned between ether and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of compound (A).

(B) (3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

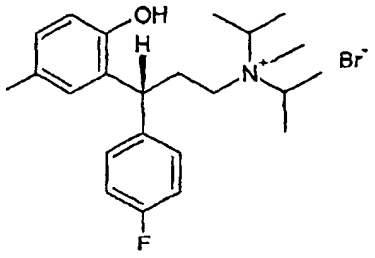
Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate, the title compound (B) is obtained.

EXAMPLE 14 (3R)-3-[2-(Isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



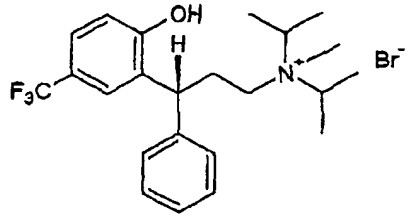
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl 2-methylpropanoate, the title compound is obtained.

EXAMPLE 15 (3R)-3-(4-Fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide



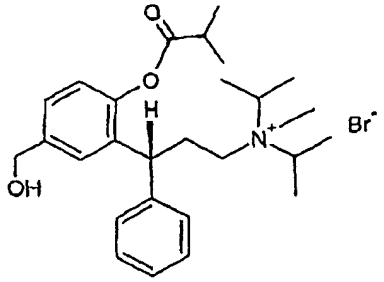
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-(4-fluorophenyl)propyl]-4-methylphenol, the title compound is obtained.

EXAMPLE 16 (3R)-3-[2-Hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



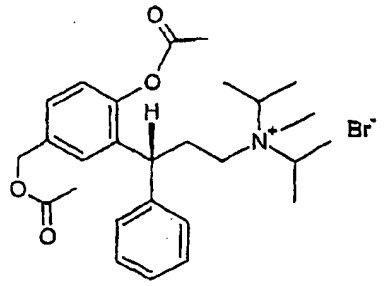
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(trifluoromethyl)phenol, the title compound is obtained.

EXAMPLE 17 (3R)-3-[2-(Isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



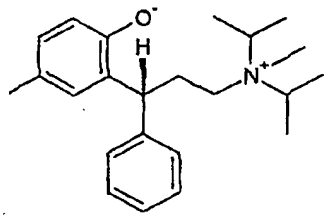
(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with isobutyryl bromide to give the title compound.

EXAMPLE 18 (3R)-3-{2-(Acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with acetyl bromide, to give the title compound.

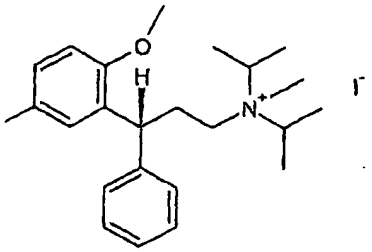
EXAMPLE 19 2-{(1R)-3-[Diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate



(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide from Example 2 is passed through an ion exchange column so as to remove the bromide ion and generate the title compound.

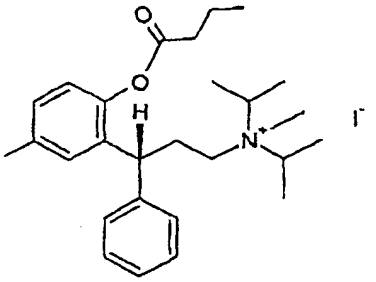
Reacting the above compound with an equivalent amount of an acid, such as methanesulfonic acid, hydrochloric acid, acetic acid, or succinic acid, generates other salts of the title compound.

EXAMPLE 20 (3R)-N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with (3R)-N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropan-1-amine, the title compound is obtained; mp 211 °C (dec). Anal Calcd for $C_{24}H_{36}INO$: C, 59.87; H, 7.54; N, 2.91. Found: C, 59.78; H, 7.56; N, 2.99. $[\alpha]_D$ (c = 1, MeOH) +13°.

EXAMPLE 21 (3R)-3-[2-(Butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate

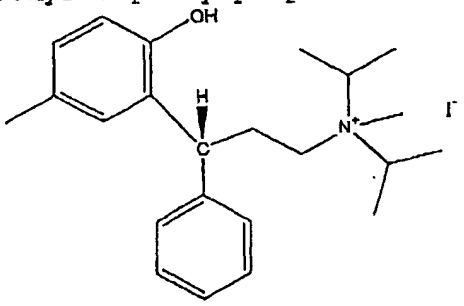
A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (1.0 g) in butyryl chloride (5 ml) is heated under reflux for 90 min. Ether is added, and the precipitate of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate hydrochloride is filtered off; mp 116-119 °C. Anal Calcd for $C_{26}H_{37}NO_2 \cdot HCl$: C, 72.28; H, 8.86; Cl, 8.21; N, 3.24. Found: C, 72.25; H, 8.71; Cl, 8.17; N, 3.25. $[\alpha]_D$ (c = 1, MeOH) +20°.

The hydrochloride salt is partitioned between ether and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of the title compound (A).

(B) (3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

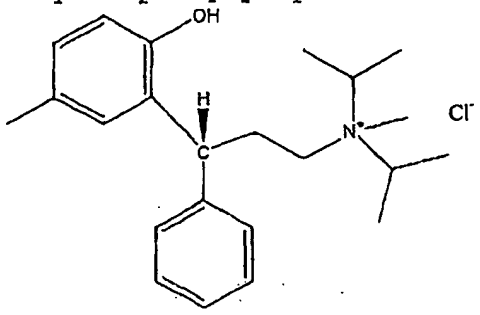
Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate, the title compound is obtained; mp 175 °C (dec). Anal Calcd for $C_{27}H_{40}INO_2$: C, 60.33; H, 7.50; N, 2.61. Found: C, 60.37; H, 7.52; N, 2.58.

EXAMPLE 22 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



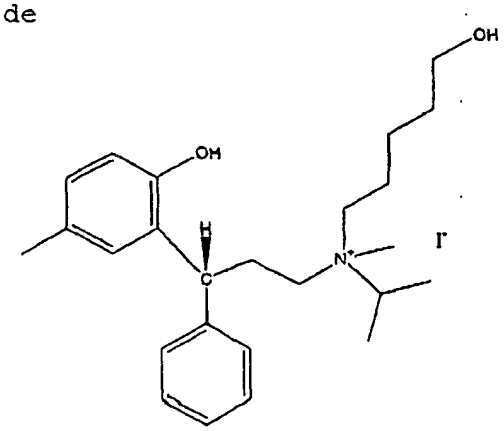
(3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide (from Example 22) was hydrolysed with methanol, resulting in the title compound.

EXAMPLE 23 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride



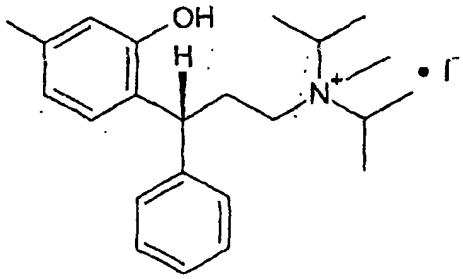
A solution of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide (4.2 g, 0.01 mol) in water (50 ml) is neutralized by addition of 1 equivalent of 2 N sodium hydroxide solution (5.0 ml). The solvent is evaporated, and the residual oil is chromatographed to separate 2-{(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate from the sodium bromide. The product is reconstituted in acetone, and a solution of hydrogen chloride in ethyl acetate is added to give a precipitate of the title compound.

EXAMPLE 24 5-Hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide



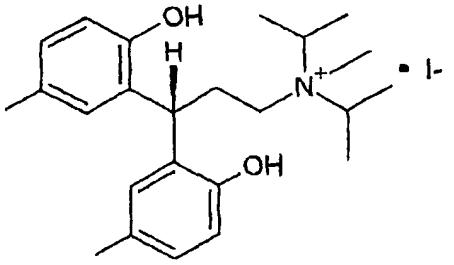
Following the general procedure of Example 2 and making non critical variations, but starting with 2-{(1R)-3-[(5-hydroxypentyl)(isopropyl)amino]-1-phenylpropyl}-4-methylphenol, the title compound is obtained.

EXAMPLE 25 (3R)-3-(2-Hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



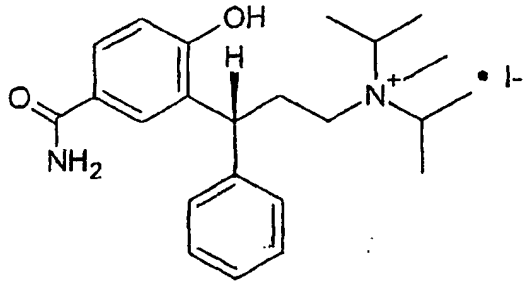
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-5-methylphenol, the title compound is obtained.

EXAMPLE 26 3,3-bis(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide



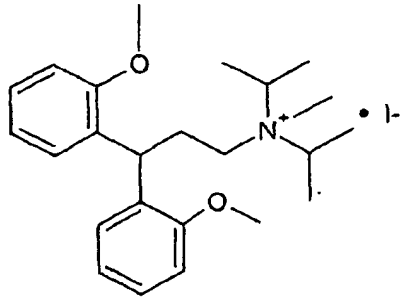
Following the general procedure of Example 2 and making non critical variations, but starting with 2-[3-(diisopropylamino)-1-(2-hydroxy-5-methylphenyl)propyl]-4-methylphenol, the title compound is obtained.

EXAMPLE 27 (3R)-3-[5-(Aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



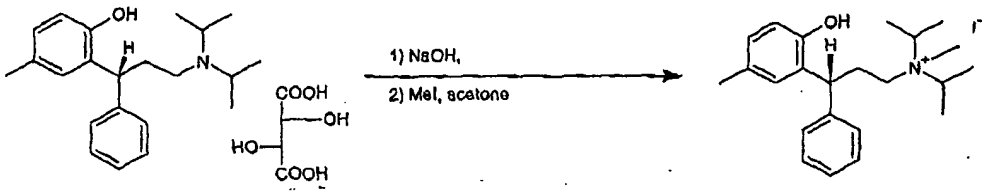
Following the general procedure of Example 2 and making non critical variations, but starting with 3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxybenzamide, the title compound is obtained.

EXAMPLE 28 3,3-bis(2-Methoxyphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with N,N-diisopropyl-3,3-bis(2-methoxyphenyl)propan-1-amine, the title compound is obtained.

EXAMPLE 29 Large scale production of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



A 5 l erlenmyer flask was charged with 250 g (526 mmol) tolterodine tartrate, water (2000 ml), and methylene chloride (2000 ml). A solution of 84 g of 50% NaOH diluted with 200 ml of water was added, and the mixture was stirred for 1 hour. The pH was kept in the range of 8-9. Both of the two resulting phases are clear and colorless.

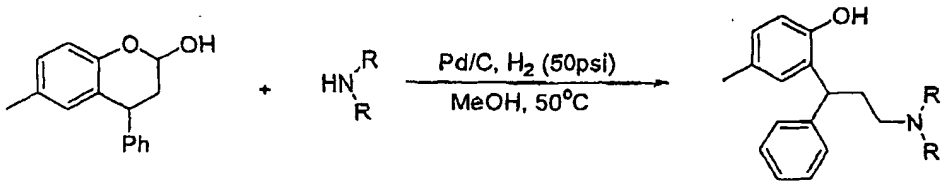
The phases were separated, and the aqueous phase was washed with methylene chloride (1000 ml). The combined organic phases were concentrated on the rotovap (60°C bath). The weight of the residue was determined. The residue was dissolved in acetone (1000 ml), and 263 ml (2.84 mol) methyl iodide was added, all in one portion. The mixture was stirred at room temperature overnight.

The resulting slurry was filtered, washed with acetone (250 ml) and dried in the vacuum oven at 50°C overnight.

This provided 230 g of the desired product, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

EXAMPLE 30 Cyclic amine intermediates

The following general reductive amination procedure was employed:



wherein Ph represents a phenyl group, and R represents an alkyl group according to the following Table I.

Briefly, palladium on activated carbon (1.76 g, 5% by weight, Aldrich 20,568-0) was charged to a hydrogenation vessel under nitrogen, followed by a MeOH (20 mL) solution of a racemic lactol (6-methyl-4-phenyl-2-chromanol, see formula above) (4 g, 16.64 mmol) and a secondary amine (42 mmol, 2.5 equiv). The vessel was filled with hydrogen (50 psi), and the reaction mixture was stirred vigorously at 50°C overnight. The heterogeneous reaction mixture was filtered through celite. The resulting methanolic solution was concentrated under vacuum.

Pure cyclic amines according to the following table I were obtained after trituration with hexanes.

Table I Intermediate compounds

R	Resulting compound	Yield (%)
$(CH_2)_4$	4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol	71
$(CH_2)_5$	4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol	33
$(CH_2)_6$	2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol	29

Characterization of 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol:

^{1}H NMR ($CDCl_3$): δ 1.90 (m, 4H), 2.09 (s, 4H), 2.25-2.45 (m, 2H), 2.57 (m, 2H), 2.63-2.78 (m, 3H), 4.55 (dd, 1H, J=12 Hz, J=3 Hz), 6.47 (s, 1H), 6.85 (s, 2H), 7.19-7.26 (m, 2H), 7.30 (m, 3H), 11.23 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 19.8, 26.0, 33.5, 39.9, 53.5, 54.3, 125.8, 127.3, 128.1, 128.4, 128.7, 131.2145.0, 153.0.

ESI mass spectrum: 296 [M+1$^+$], 297 [M+2$^+$].

Characterization of 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol:

^{1}H NMR ($CDCl_3$): δ 1.52-1.53 (m, 2H), 1.62-1.81 (m, 4H), 1.98 (t, 1H, J=10 Hz), 2.09 (s, 3H), 2.26-2.60 (m, 6H), 4.46 (dd, 1H, J=13 Hz, J=3 Hz), 6.47 (s, 1H), 6.85 (d, 2H, J=0.9 Hz), 7.19-7.24 (m, 2H), 7.30-7.35 (m, 3H), 11.24 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 20.9, 24.4, 25.4, 31.3, 38.4, 53.8, 54.7, 61.0, 102.2, 117.9, 126.3, 128.1, 128.4, 128.6, 129.3, 129.4, 131.4, 145.2, 154.3.

ESI mass spectrum: 310 [M+1$^+$], 311 [M+2$^+$]

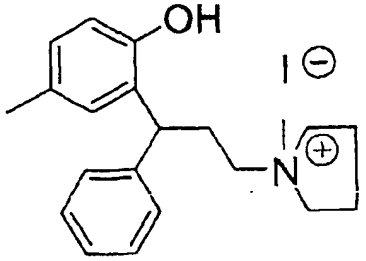
Characterization of 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol;

^{1}H NMR ($CDCl_3$): δ 1.60-1.65 (m, 4H), 1.65-1.85 (m, 4H), 1.95-2.10 (m, 4H), 2.30-2.67 (m, 6H), 2.70-2.80 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 19.6, 26.6, 26.7, 32.0, 40.7, 55.1, 55.7, 115.9, 125.8, 127.3, 128.0, 128.1 128.5, 128.7, 131.4, 145.1, 153.0, 145.2, 152.8.

ESI mass spectrum: 324 [M+1$^+$], 325 [M+2$^+$].

EXAMPLE 31 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 79%. The resulting compound was characterized:

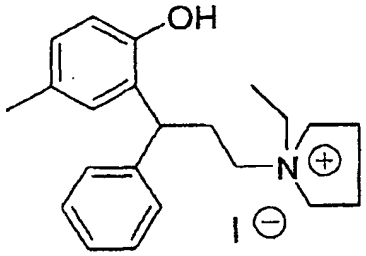
^{1}H NMR (MeOH-d_4): δ 2.05-2.18 (m, 4H), 2.20 (s, 3H), 2.46-2.62 (m, 2H), 3.08 (s, 3H), 3.14-3.40 (m, 2H), 3.40-3.62(m, 4H), 4.40 (t, 1H, J=7.3 Hz), 6.68 (d, 1H, J=8Hz), 6.85 (d, 1H, J=8 Hz), 6.98 (d, 1H, J=1.5 Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, J=7 Hz), 7.37-7.42 (m, 2H).

^{13}C NMR (MeOH-d_4): δ 19.3, 21.5, 28.2, 41.5, 46.8, 63.6, 64.5, 115.2, 126.5, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.5.

Elemental analysis, $C_{21}H_{28}INO$: Found(%): C 57.64, H 6.43, I 28.77, N 3.23, O 3.88; Theory(%): % C 57.67, H 6.45, I 29.02, N 3.20, O 3.66.

ESI mass spectrum for $C_{21}H_{28}NO^+$: 310.2.

EXAMPLE 32 1-Ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide



Ethyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred

overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 81%. The resulting compound was characterized:

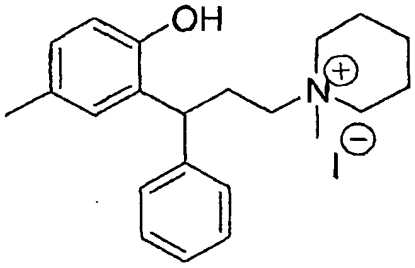
^{1}H NMR (MeOH-d_4): δ 1.24 (t, 3H, J=7 Hz), 2.0-2.18 (m, 4H), 2.20 (s, 3H), 2.40-2.63 (m, 2H), 3.08-3.25 (m, 2H), 3.35-3.60 (m, 6H), 4.38 (t, 1H, J=7.5 Hz), 6.70 (d, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 7.0 (d, 1H, J=1.4 Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, J=7 Hz), 7.37-7.42 (m, 2H).

^{13}C NMR (MeOH-d_4): δ 8.0, 19.5, 21.5, 28.0, 41.9, 54.7, 58.0, 64.5, 117.8, 126.4, 127.9, 128.1, 128.4, 128.7, 128.9, 129.2, 143.6, 152.8.

Elemental analysis, $C_{22}H_{30}INO$: Found(%): C 58.17, H 6.65, I 27.79, N 3.10, O 3.62; Theory(%): C 58.54, H 6.70, I 28.11, N 3.10, O 3.54.

ESI mass spectrum for $C_{22}H_{30}NO^+$: 324.2.

EXAMPLE 33 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide



Methyl iodide (3.42 g, 1.5 mL, 0.024 mol) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol of Example 30 (0.3 g, 0.97 mmol) in a mixture of acetonitrile (6 mL) and acetone (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate

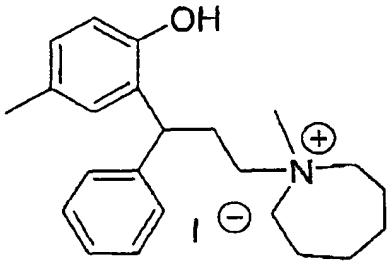
precipitation of the resulting quaternary ammonium salt. The white precipitate was filtered out, washed with chloroform and diethyl ether and dried under vacuum to give 0.397 g (90%) of the title compound.

Characterization of the obtained compound:

^{1}H NMR (MeOH-d_4): δ 1.57-1.84 (m, 6H), 2.19 (s, 3H), 2.46-2.64 (m, 2H), 3.06 (s, 3H), 3.14-3.4 (m, 6H), 4.39 (t, 1H, J=7.3Hz), 6.68 (d, 1H, J=8 Hz), 6.85 (dd, 1H, J=8 Hz, J=1.5 Hz), 7.0 (d, 1H, J=1.5 Hz), 7.18 (t, 1H, J=8Hz), 7.29 (t, 1H, J=7.4 Hz), 7.37-7.4 (m, 5H).

^{13}C NMR MeOH-d_4): δ 19.5, 19.7, 19.8, 20.7, 26.7, 41.5, 60.9, 61.2, 114.0, 115.1, 126.3, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.4.

EXAMPLE 34 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol of Example 30 (0.3 g, 1.02 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate precipitation of the resulting quaternary ammonium salt. The white precipitate was filtered out, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 77%. The resulting compound was characterized:

^{1}H NMR (MeOH-d_4): δ 1.6-2.0 (m, 8H), 2.01 (s, 3H), 2.40-2.70 (m, 2H),), 3.10 (s, 3H), 3.15-3.60 (m, 6H), 4.38 (t,

1H, J=7 Hz), 6.68 (d, 1H, J=8Hz), 6.88 (d, 1H, J=8 Hz), 7.05 (s, 1H), 7.18-7.24 (m, 1H), 7.25-7.40 (m, 5H).
^{13}C NMR (MeOH-d_4): δ 20.8, 22.4, 27.5, 41.6, 50.2, 59.2, 63.8, 64.5, 64.8, 117.5, 126.3, 127.95, 128.03, 128.4, 128.6, 128.9, 129.2, 143.4, 152.5.
ESI mass spectrum for $C_{23}H_{32}NO^+$: 338.2.

The usefulness of the compounds according to the invention is further illustrated by the following examples.

EXAMPLE I Binding data

Muscarinic receptor subtype M_1-M_5 binding assays were carried out. Briefly, [3]H-methylscopolamine was allowed to bind to membranes from various recombinant mammalian cell lines, each with an over-expression of a particular receptor subtype. An equilibrium radioligand displacement assay was performed using the title compound of example 2, (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide (a quaternary ammonium compound according to the invention), and for comparison the following anticholinerigic agents: tolterodine, hydroxytolterodine, ipratropium, and atropine. The resulting K_i values, displayed in Table II, are averages of duplicate samples at each dose in an 11-point dose-response curve, using half-log intervals.

Table II K_i values (nM)

Receptor subtype	Displacing compound				
	(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide	Tolterodine	Hydroxytolterodine	Ipratropium	Atropine
M_1	0.33	0.87	1.5	0.46	0.25
M_2	0.45	0.73	0.33	0.17	0.43
M_3	0.20	2.1	1.4	0.38	0.87
M_4	0.39	1.5	1.4	0.42	0.48
M_5	0.25	0.55	0.48	0.54	0.47

Thus, the title compound of example 2, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, according to the invention has high affinity and little or no selectivity for any of the muscarinic receptor M_1-M_5 subtypes. Obtained K_i values for (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide are in the same range as K_i values for tolterodine, hydroxytolterodine, ipratropium, and atropine.

EXAMPLE II Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Compounds for aerosol administration were prepared in sterile Dulbecco's Phosphate Buffered Saline.

Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Ten minutes, 4 hours, 8 hours, 24 hours, 36 hours or 48 hours later, the mice were moved to whole body plethysmograph chambers. Bronchoconstriction was induced in mice by administration of an 80 mg/ml methacholine (MC) aerosol into the plethysmograph chambers for 5 minutes. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation treatment with vehicle, or 80 mg/ml methacholine following inhalation treatment with 0.072, 0.144, or 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation treatment with 1.24 mg/ml ipratropium bromide. The average enhanced pause (lung resistance) was determined. In order to determine the baseline, saline aerosol (without methacholine) was also separately administered to the mice.

The results are shown in fig 1 (1.44 mg/ml of the title compound of example 2 and 1.24 mg/ml ipratropium bromide), fig 2 (0.144 mg/ml of the title compound of example 2), and fig 3 (0.072 mg/ml of the title compound of example 2).

Increasing doses of the title compound of example 2 produce increasing durations of action. In fig 1, inhalation of aerosols generated from a solution containing 1.44 mg/ml of the title compound of example 2 produced a complete block of methacholine-induced bronchoconstriction through 36 hours following administration. Ipratopium bromide (1.24 mg/ml) did not

display an equally sustained action. Inhalation of aerosols generated from solutions containing 0.144 mg/ml (fig 2) or 0.072 mg/ml (fig 3), respectively, of the title compound of example 2 prevented methacholine-induced bronchoconstriction through 24 or 8 hours, respectively, following administration.

EXAMPLE III Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

Ten minutes, 30 minutes, 1 hour, 2 hours or 4 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation treatment with 1.46 mg/ml tolterodine, or 80 mg/ml methacholine following inhalation treatment with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

The results are shown in fig 4. It is obvious from fig 4 that the title compound of example 2 has a pronounced effect on lung resistance. In addition, the bronchodilatory effects of the title compound of example 2 exhibit a prolonged duration.

EXAMPLE IV Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

Ten minutes, 2 hours, 4 hours, 8 hours or 24 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation with 1.24 mg/ml ipratropium bromide.

The results are shown in fig 5. It can be concluded that the bronchodilatory effects of the title compound of example 2 have a longer duration when compared to ipratropium bromide.

EXAMPLE V Pharmacokinetics of inhaled quaternary ammonium salts in Balb/c mice

Blood samples were taken from the mice in example II via cardiac puncture under isoflurane anesthesia at 2.5 minutes, 10 minutes, 30 minutes, 2 hours, 4 hours, 8 hours, or 12 hours after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels of the title compound of example 2 were determined by ESI-LC/MS/MS using a PE SCIEX API 4000 mass spectrometer in positive ion mode. Chromatographically, the analyte and the internal standard were resolved on a Phenomenex Phenyl-Hexyl column using an isocratic elution. The limit of quantitation was 24 pg/ml.

Plasma concentrations of the title compound of example 2 following aerosol exposure (inhalation) are summarized in table III and fig 6.

Table III Plasma concentration

Time	Plasma concentration ± std dev (pg/ml) following inhalation of various conc.		
	0.072 mg/ml	0.144 mg/ml	1.44 mg/ml
2.5 min	136 ± 38	264 ± 21	2675 ± 389
10 min	90 ± 1	162 ± 11	1395 ± 163
30 min	81 ± 8	112 ± 10	1120 ± 42
2 h	41 ± 6	55 ± 7	245 ± 3
4 h	14 ± 1	40 ± 3	157 ± 2
8 h	-	12 ± 1	80 ± 2
12 h	-	-	42 ± 2

The doses given to the lungs were proportional to the concentrations appearing in the plasma. Importantly, the systemic (plasma) exposure was very low, which indicates that the title compound of example 2 resides for a prolonged time in the lung. This correlates well with its long duration of action.

EXAMPLE VI (comparative) Pharmacokinetics of inhaled tolterodine in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml, and administered to the mice (aerosol) as in example II.

Blood samples were collected at 2.5 minutes, 15 minutes, 30 minutes, 1 hour or 2 hours after aerosol drug treatment. Blood samples were prepared as in example VI. Samples were analyzed using a PE SCIEX API 3000 mass spectrometer. Chromatographically, the analyte and the internal standard were resolved on a Zorbax ACE Phenyl column using a gradient elution. The limit of quantitation was 100pg/mL.

Figure 7 shows plasma concentrations of tolterodine following inhalation of nebulized solutions at 0.1, 0.5, or 1.0 mg/ml. Plasma levels for the 0.1 mg/ml concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation. The plasma level of tolterodine is approximately one order of magnitude higher than the corresponding level of the the title compound of example 2 (example V, fig 6).

This demonstrates that while tolterodine is rapidly spread systemically, the compounds according to the invention have an increased duration of action, with implications locally (i.e. for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, or rhinorrhea due to the common cold).

EXAMPLE VII Binding data

Muscarinic receptor subtype M_1-M_5 binding assays were performed. K_i values were determined for the title compounds of examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention). The resulting K_i values are displayed in Table IV.

Table IV K_i values (nM)

Receptor subtype	Title compound of Example no					
	3	8	31	32	33	34
M_1	0.3	0.86	1.2	1.1	1.1	1
M_2	0.52	1.08	2.2	1.7	1.7	1
M_3	0.43	0.92	3.3	3.1	3.2	4.7
M_4	0.72	1.07	4.2	3.8	3.6	2.9
M_5	0.26	0.68	1.6	1.2	0.9	1.8

Thus, the title compounds of Example nos 3, 8, and 31-34 according to the invention have high affinity and little or no selectivity for any of the muscarinic receptor M_1-M_5 subtypes.

EXAMPLE VIII Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Bronchoconstriction was induced in BALB/c mice by administration of methacholine. The title compounds of Examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention) were administered to the mice via inhalation of 1 mg/mL (free base equivalents (FBE)) of each compound. The resulting inhibition of methacholine-induced bronchoconstriction was determined at 10 min as well as 24 h and 48 h, or 36 h, after dosing. The results are displayed in the following Table V.

Table V

Title compound of example no (1 mg/mL FBE)	% inhibition of bronchoconstriction after 10 min	24 h	36 h	48 h
3	100		93	
8	82	60		15
31	100		0	
32	100		17	
33	100		0	
34	100		0	

EXAMPLE A

A 65 year old female with a history of chronic COPD with FEV_1 of 1.5 liters is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 1 mg every 12 hr continuously for dyspnea. After two weeks of therapy, dyspnea tolerance is improved.

EXAMPLE B

A 50 year old male with a history of chronic COPD with FEV_1/FVC of 60% is treated with (3R)-3-(2-hydroxy-5-

methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide in an aerosol formulation, 2 mg every 8 hr continuously for dyspnea. After a week of treatment, the FEV_1/FVC ratio improves to about 65%.

EXAMPLE C

A 25 year old female with a history of asthma with a morning peak flow of less than 2 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide powder, 0.1 mg every 8 hr continuously. Treatment improves the peak flow to 4-5 l/sec.

EXAMPLE D

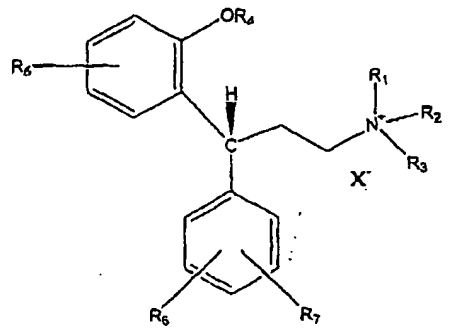
A 35 year old male with a history of severe asthma with a morning peak flow of 5 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide powder, 6 mg once a day continuously. After a week of treatment, the peak flow improves to 9 l/sec.

EXAMPLE E

A 45 year old female with a history of severe asthma with a morning peak flow of less than 3 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 2 mg three times daily continuously. After a week of treatment the peak flow improves to 6 l/sec.

CLAIMS

1. A quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1, R_2 and R_3 independently represent C_1-C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1, R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 represents

-H,

$-CH_3$, or

$-CO-R_{4-1}$, wherein R_{4-1} represents

$-(C_1-C_4$ alkyl),

$-(C_1-C_4$ alkoxy), or

$-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent -H or $-(C_1-C_4$ alkyl);

R_5, R_6 and R_7 independently represent

-H,

$-OCH_3$,

-OH,

$-CONH_2$,

$-SO_2NH_2$,

-F, -Cl, -Br, -I,

$-CF_3$, or

$-(C_1-C_4$ alkyl), optionally substituted with one or two

-OH,

-(C_1-C_4 alkoxy),

-COOH, or

-CO-O-(C_1-C_3 alkyl); and

X^- represents an anion of a pharmaceutically acceptable acid.

2. A quaternary ammonium compound according to claim 1, wherein the carbon stereocenter is (R).

3. A quaternary ammonium compound according to claim 1, wherein the carbon stereocenter is (S).

4. A quaternary ammonium compound according to claim 1, which is a mixture of stereoisomers.

5. A quaternary ammonium compound according to claim 1, wherein at least one of R_1, R_2 and R_3 represents C_1-C_3 alkyl.

6. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents isopropyl.

7. A quaternary ammonium compound according to claim 6, wherein at least two of R_1, R_2 and R_3 represents isopropyl.

8. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents methyl.

9. A quaternary ammonium compound according to claim 5, wherein at least one of R_1, R_2 and R_3 represents ethyl.

10. A quaternary ammonium compound according to claim 1, wherein R_1 and R_2 jointly form a ring together with the quaternary ammonium nitrogen.

11. A quaternary ammonium compound according to claim 10, wherein said ring comprises from 4 to 6 carbon atoms.

12. A quaternary ammonium compound according to claim 1, wherein R_4 represents -H, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents C_1-C_4 alkyl.

13. A quaternary ammonium compound according to claim 12, wherein R_4 represents -H.

14. A quaternary ammonium compound according to claim 1, wherein R_5 represents -H, -Br, -Cl, $-CH_3$, or $-CH_2OH$.

15. A quaternary ammonium compound according to claim 14, wherein R_5 represents $-CH_3$.

16. A quaternary ammonium compound according to claim 1, wherein at least one of R_6 and R_7 represents -H.

17. A quaternary ammonium compound according to claim 1, wherein both R_6 and R_7 represent -H.

18. A quaternary ammonium compound according to claim 1, wherein X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, HOOC-CH=CH-COOH, and benzoic.

19. A quaternary ammonium compound according to claim 18, wherein X^- is selected from the group consisting of iodide, bromide, and chloride.

20. A quaternary ammonium compound according to claim 19, wherein X^- represents iodide.

21. A quaternary ammonium compound according to claim 19, wherein X^- represents chloride.

22. A quaternary ammonium compound according to claim 19, wherein X^- represents bromide.

23. A quaternary ammonium compound according to claim 1, which is selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-N-ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide,

(3R)-N-benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,

(3R)-N-(tert-butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-(5-chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-(5-bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-[2-(isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(4-fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide,

(3R)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-[2-(isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-3-{2-(acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

2-{(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate,

(3R)-N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride,

5-hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide,

(3R)-3-(2-hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

3,3-bis(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide,

(3R)-3-[5-(aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

3,3-bis(2-methoxyphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide,

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide,

1-ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide,

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide, and

1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide.

24. A quaternary ammonium compound according to claim 23, which is selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide, and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

25. A pharmaceutical composition comprising a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24, and a suitable pharmaceutical carrier therefor.

26. A quaternary ammonium compound according to any one of claims 1-24 for use as a medicament.

27. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating asthma.

28. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD).

29. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating rhinorrhea due to the common cold.

30. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating allergic rhinitis.

31. A method of treating asthma in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

32. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

33. A method of treating allergic rhinitis in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

34. A method of treating rhinorrhea due to the common cold in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a

quaternary ammonium compound according to any one of claims 1-24.

Drawings

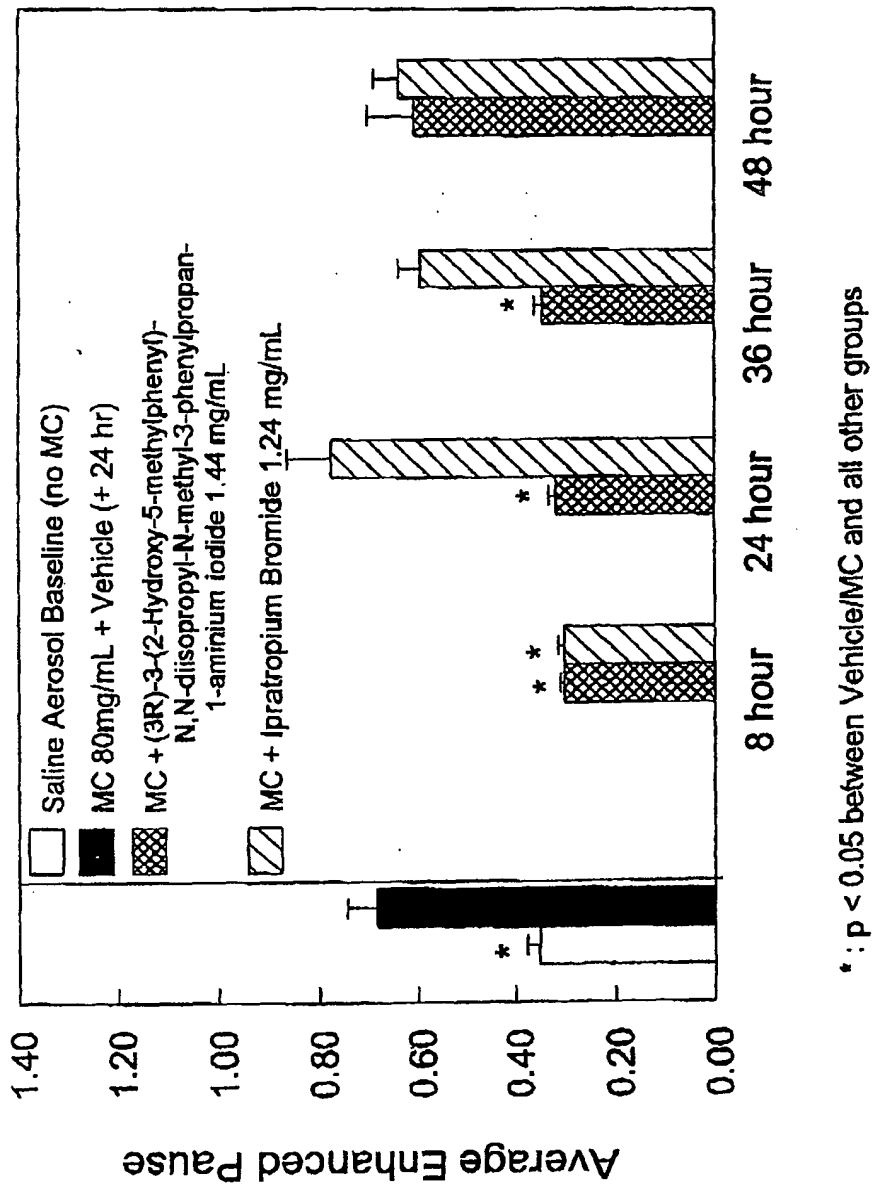


FIGURE 1

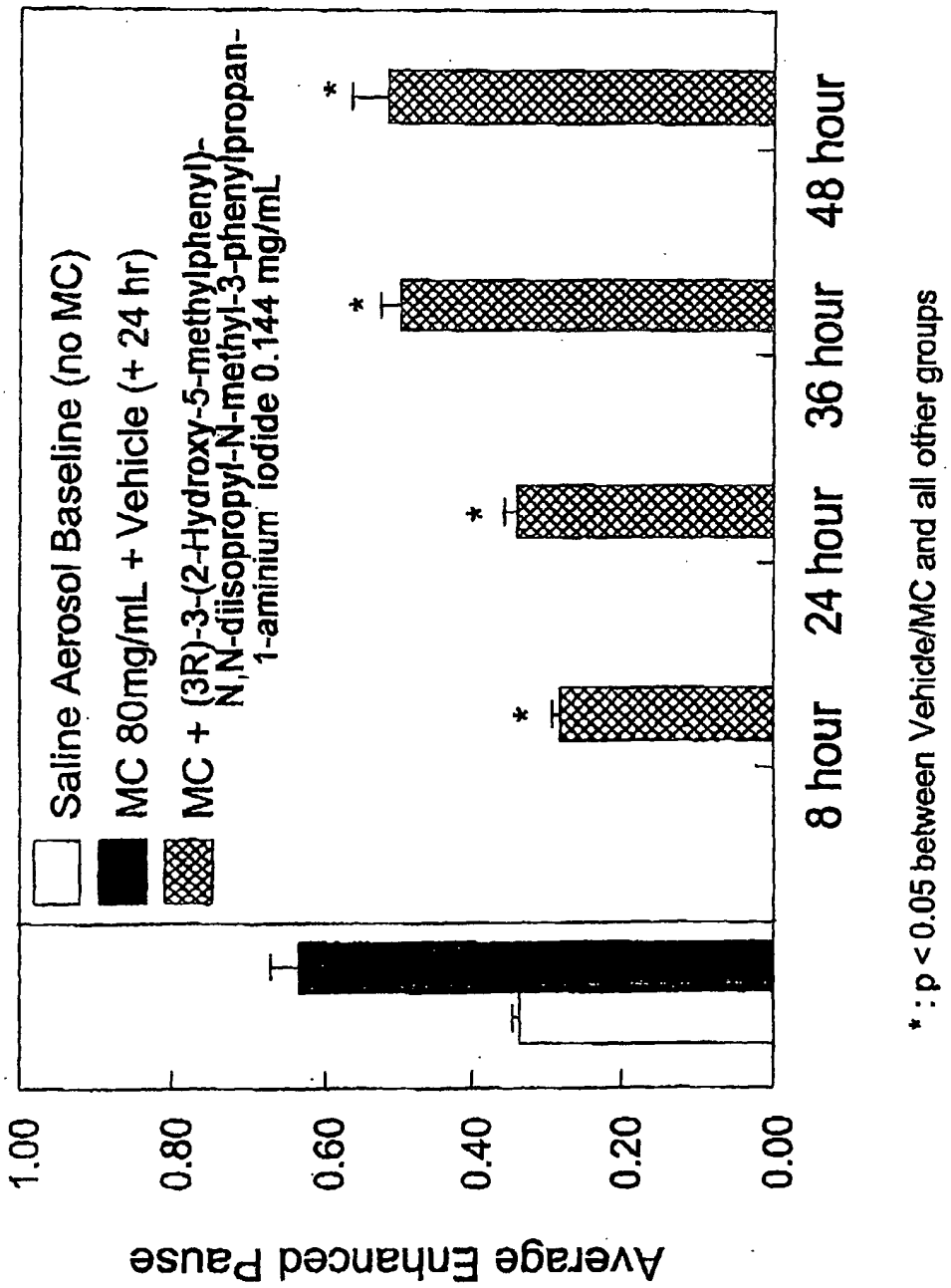

Saline Aerosol Baseline (no MC)
MC 80mg/mL + Vehicle (+ 24 hr)
MC + (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide 0.144 mg/mL
Average Enhanced Pause
1.00
0.80
0.60
0.40
0.20
0.00
8 hour
24 hour
36 hour
48 hour
*
*
*
*
*: p < 0.05 between Vehicle/MC and all other groups

FIGURE 2

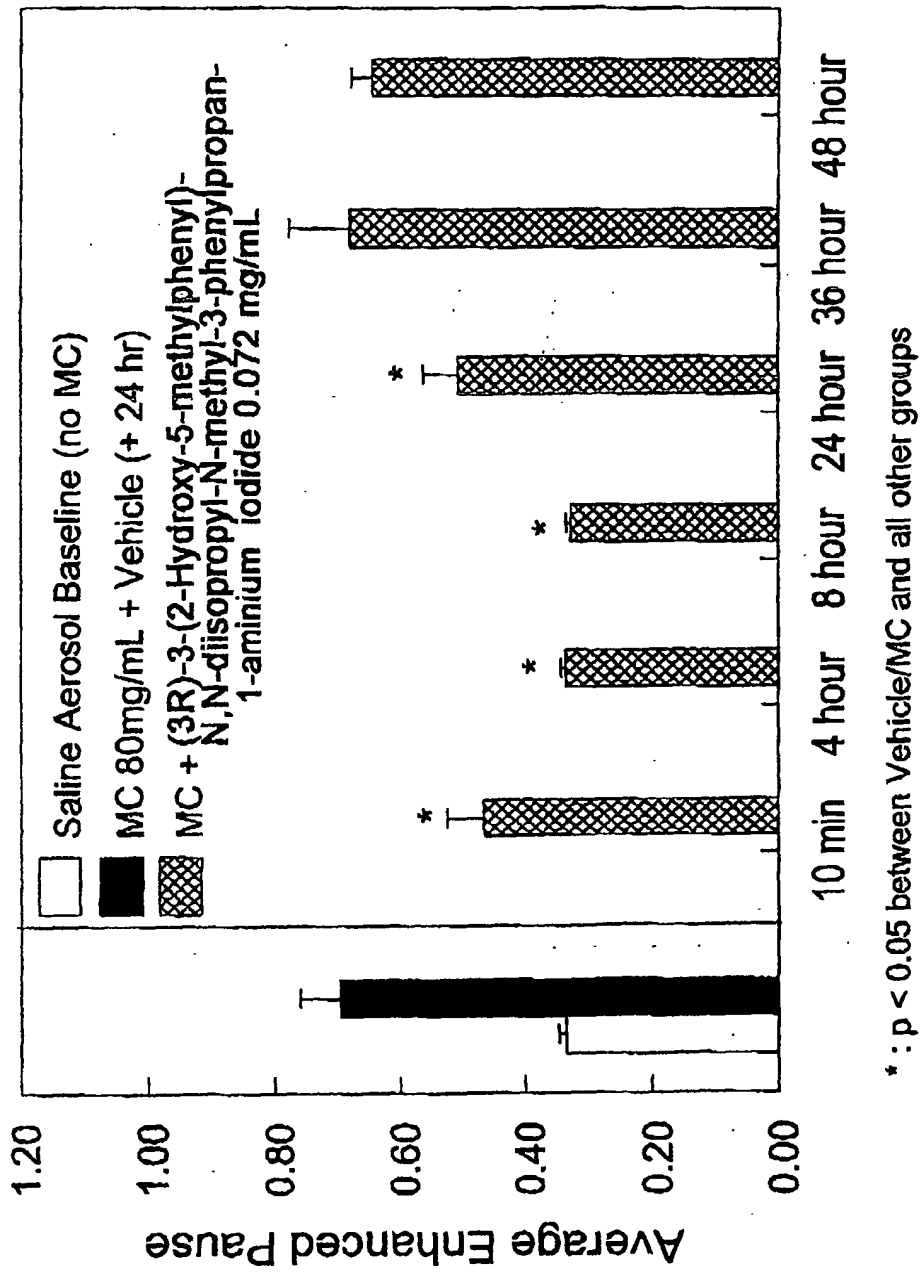

Saline Aerosol Baseline (no MC)
MC 80mg/mL + Vehicle (+ 24 hr)
MC + (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide 0.072 mg/mL
Average Enhanced Pause
1.20
1.00
0.80
0.60
0.40
0.20
0.00
10 min
4 hour
8 hour
24 hour
36 hour
48 hour
*
*
*
*
* : p < 0.05 between Vehicle/MC and all other groups

FIGURE 3

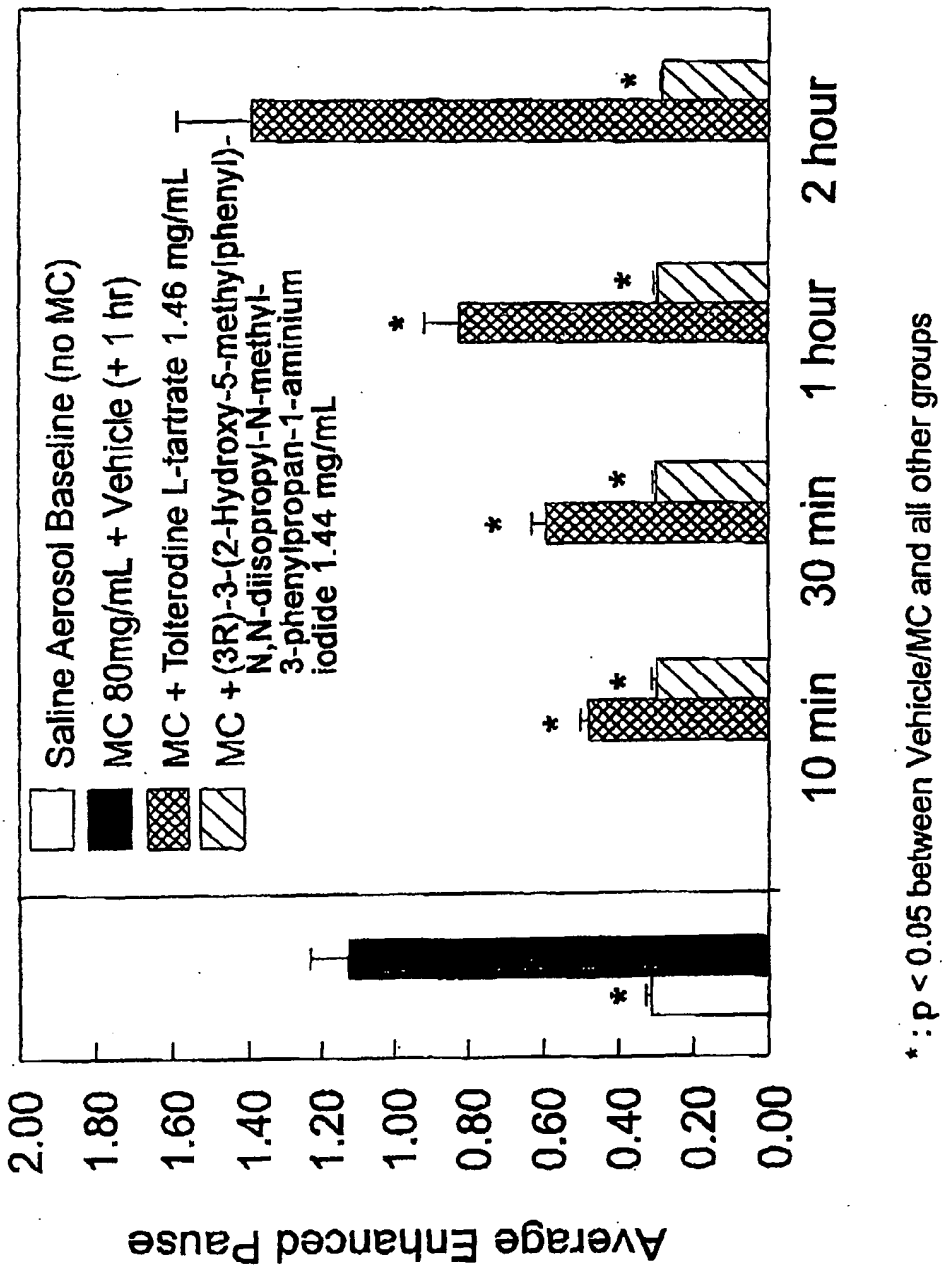

Saline Aerosol Baseline (no MC)
MC 80mg/mL + Vehicle (+ 1 hr)
MC + Tolterodine L-tartrate 1.46 mg/mL
MC + (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide 1.44 mg/mL
Average Enhanced Pause
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
10 min
30 min
1 hour
2 hour
*
* : p < 0.05 between Vehicle/MC and all other groups

FIGURE 4

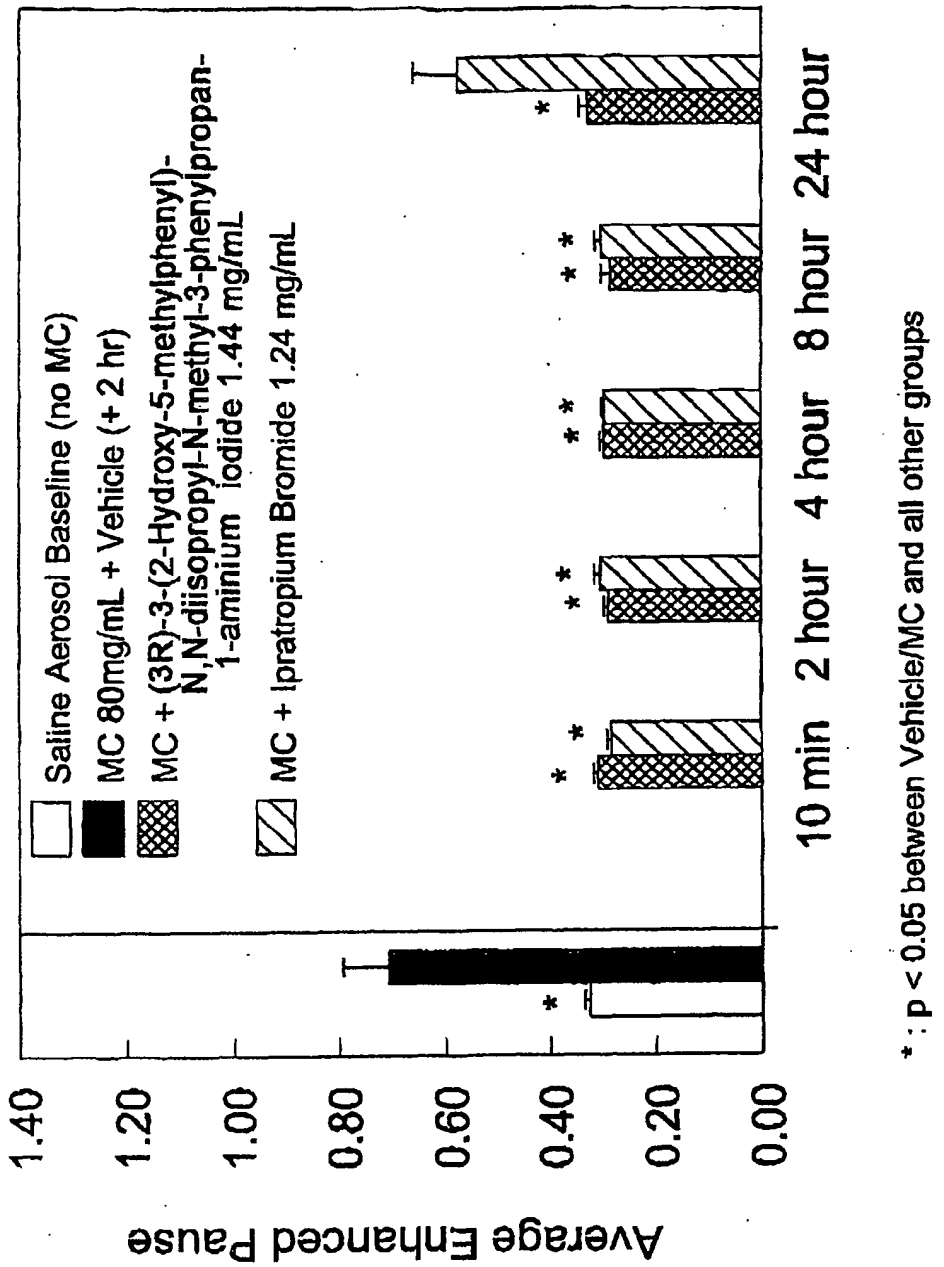


FIGURE 5

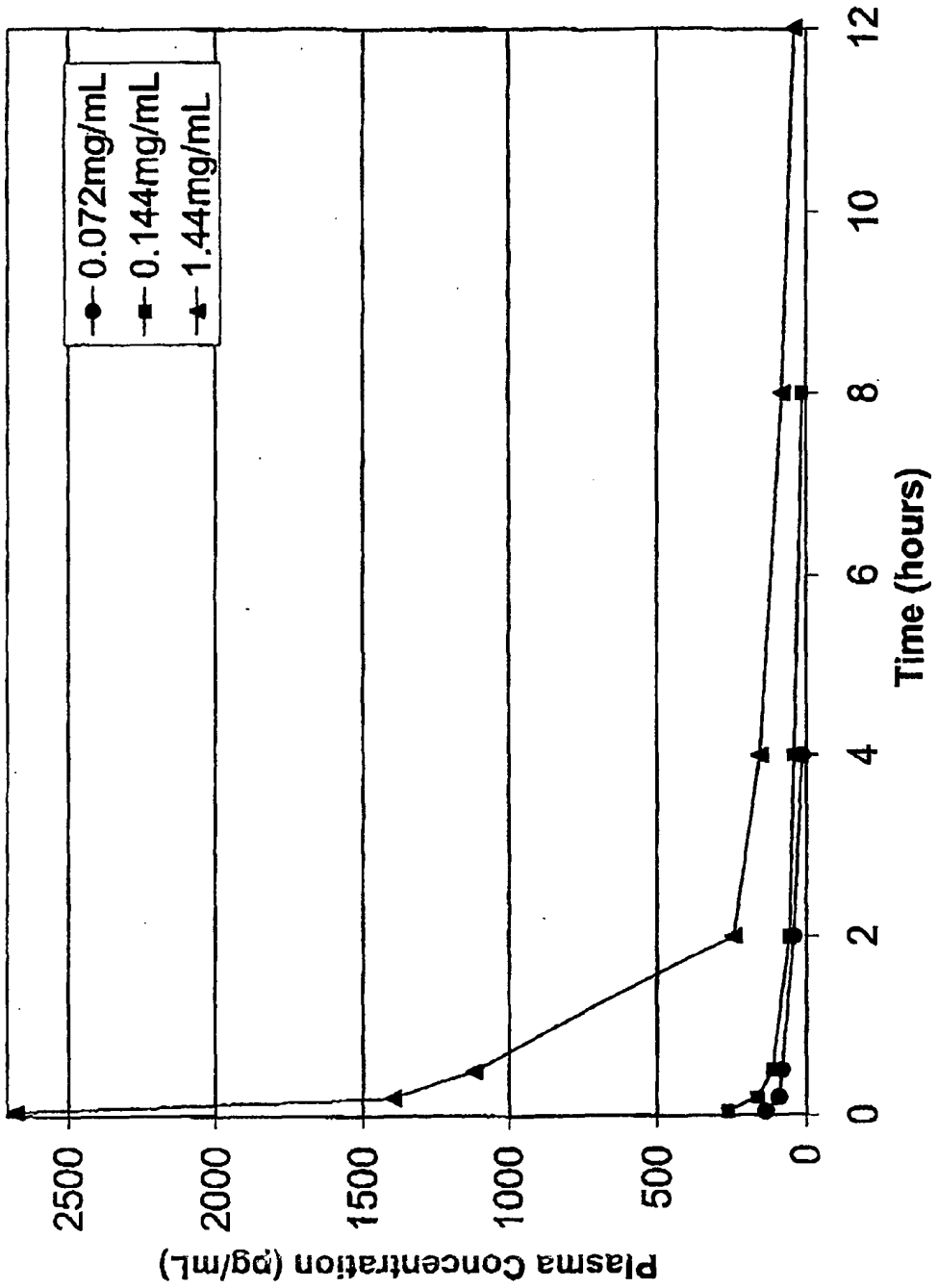


FIGURE 6

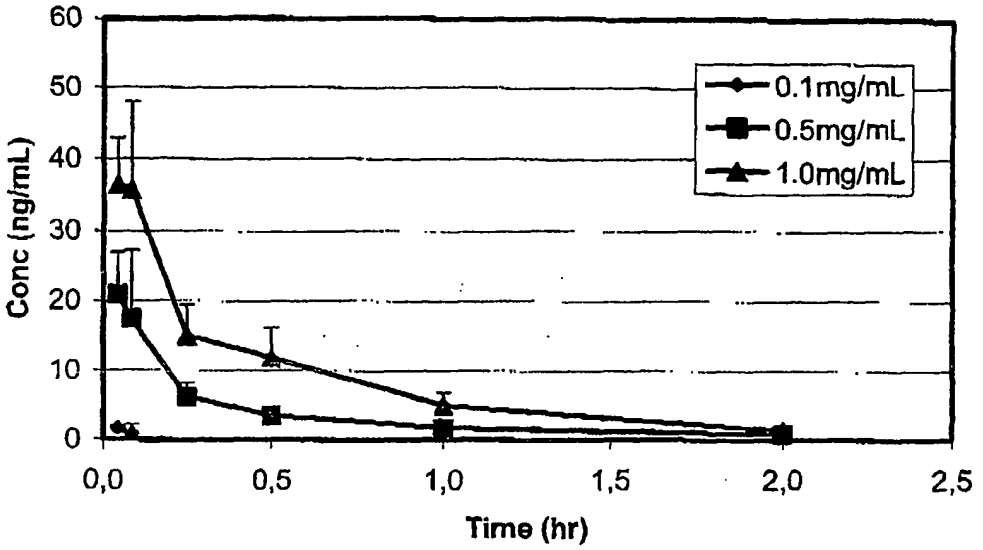


FIGURE 7

INTERNATIONAL SEARCH REPORT

Interna ...lication No
PCT/US 02/34529

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C211/27 C07C211/29 C07C215/54 C07C215/66 C07C219/28
C07D295/02 C07C217/62 A61K31/14 A61K31/452 A61K31/40
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2 592 191 A (WAYNE RUDDY ARLO) 8 April 1952 (1952-04-08) column 1, line 1 - line 11; claims	1-34
A	US 5 382 600 A (JOENSSON NILS A ET AL) 17 January 1995 (1995-01-17) cited in the application column 31 -column 36; claims; table 1	1-34
A	WEBER R W: "ROLE OF ANTICHOLINERGICS IN ASTHMA" ANNALS OF ALLERGY, AMERICAN COLLEGE OF ALLERGY AND IMMUNOLOGY,, US, vol. 65, November 1990 (1990-11), pages 348-360, XP000979858 ISSN: 0003-4738 the whole document	27-34

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2003	02/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/US 02/34529

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 5382600 A	17-01-1995	AT 65990 T	15-08-1991
		AU 635493 B2	25-03-1993
		AU 2932989 A	11-08-1989
		CA 1340223 A1	15-12-1998
		DE 68900180 D1	12-09-1991
		DK 172590 A	19-07-1990
		EP 0325571 A1	26-07-1989
		EP 0354234 A1	14-02-1990
		ES 2029384 T3	01-08-1992
		FI 109900 B1	31-10-2002
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		JP 2664503 B2	15-10-1997
		JP 3503163 T	18-07-1991
		LU 90259 A9	16-09-1998
		NO 903085 A ,B,	11-07-1990
		WO 8906644 A1	27-07-1989

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4 November 2002 (04.11.2002)

(25) Filing Language: English

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(30) Priority Data:
60/337,298 5 November 2001 (05.11.2001) US

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(72) Inventors; and
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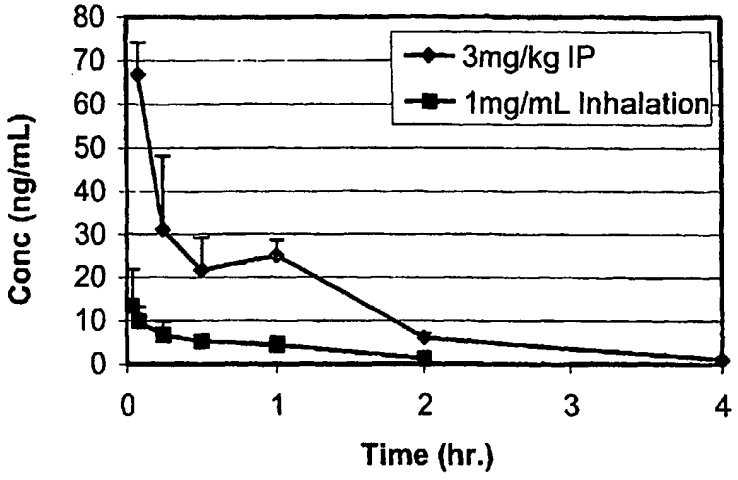
(74) Agents: **KOZLOWSKI, Holly, D.**, et al.; Dinsmore & Shohl LLP, 1900 Chemed Center, 255 East Fifth Street, Cincinnati, OH 45202 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,

[Continued on next page]

(54) Title: ANTIMUSCARINIC AEROSOL



(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a. treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation. Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor. The invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

WO 03/039464 A2

TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANTIMUSCARINIC AEROSOL

This application claims the benefit of US Provisional Patent Application No 60/337,298, filed 5 November 2001, the entire disclosure of which is herein incorporated by reference.

Technical Field

The present invention is within the field of urology. More specifically, it is generally based on the use of antimuscarinic agents for the treatment of urinary disorders, said antimuscarinic agents being administered by inhalation or insufflation.

Background of the Invention

Urinary disorders and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or

overactive bladder has been based on muscarinic receptor antagonists.

The reason why the bladder muscle contracts inappropriately is unclear in many cases. For some people it may be due to a problem with the nerve signals that run from the brain to the bladder. Sometimes minor nerve damage is caused by surgery or childbearing. This muscle squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine fills the bladder, the detrusor contracts while the bladder is filling with urine. This causes a person to feel a sudden and sometimes overwhelming urge to urinate even when the bladder is not full.

US Patent 5,382,600 discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl)-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as being useful to treat urinary incontinence. H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major, active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine.

US Patent 5,559,269 and H Postlind *et al*, Drug Metabolism and Disposition, 26(4): 289-293 (1998) disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity. The international patent application WO 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The international patent application WO 98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related to urinary incontinence.

US Patent 6,124,354 discloses 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate and its use in treating urinary incontinence and irritable bowel syndrome (see Example 99). Can. J. Chem., 40: 1909-1916 (1962) refers to this compound as a potential antidote for treatment of anticholinesterase poisoning. J. Am. Chem. Soc., 69: 2902-2906 (1947), while not mentioning the diisopropylamino compound but a diethylamino analog, discloses that the diethylamino compound has antispasmolytic action against acetylcholine.

While efficiently relieving urinary incontinence in affected patients, the above-mentioned commercially available compounds do not provide their effects instantly upon administration thereof to the patient. Since urinary disorder symptoms often have a rapid onset, it is desirable to relieve the symptoms instantly.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg, 2 mg or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms, especially when the need for medicament treatment is urgent and/or when the patient has an active life-style.

Hence, known treatments are insufficient to certain groups of patients, which demand a more flexible treatment to meet their active way of life.

There is a need for new delivery forms of antimuscarinic agents for treatment of urinary disorders, which delivery forms possess properties such that the mentioned problems can be overcome.

Summary of the Invention

For these and other purposes, it is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method brings instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method involves alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method is compatible with an active life-style.

It is a further object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is appropriate for alternative delivery forms being particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, use of which is compatible with an active life-style.

Another object of the present invention is to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament is appropriate for alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

Yet another object of the present invention is to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament is compatible with an active life-style.

For these and other objects which will be evident from the following disclosure, the present invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

The invention is based on the insight that antimuscarinic agents are rapidly distributed to the systemic circulation upon delivery via inhalation or insufflation, thus providing their effects instantly at target organs, such as the smooth muscles regulating emptying of the urinary bladder.

In one preferred embodiment of the method according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the method according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol formulation.

In yet another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.

In a preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

In a preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

In a more preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

In the most preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

In one preferred embodiment of the composition according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the composition according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the composition according to the invention, said composition is an aerosol formulation.

In yet another preferred embodiment of the composition according to the invention, said composition is a powder formulation.

In one preferred embodiment of the composition according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

In a preferred embodiment of the composition according to the invention, said antimuscarinic agent is present in an amount of from about 0.05 mg to about 12 mg, preferably from about 0.1 to about 6 mg, and more preferably from about 0.2 to about 5 mg.

The present invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

In one preferred embodiment of the use according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the use according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the use according to the invention, said medicament is an aerosol formulation.

In yet another preferred embodiment of the use according to the invention, said medicament is a powder formulation.

In a preferred embodiment of the use according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-

phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

Brief Description of the Drawings

Figure 1 is a diagram showing the plasma concentration (ng/ml)of tolterodine with time (hours) upon systemic and local administration (aerosol) in mice.

Figure 2 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) upon local administration (aerosol) of various amounts in mice.

Figure 3 is a diagram showing the variation of serum concentration (nmol/l) of tolterodine and its active metabolite with time (hours) during 9 hours upon administration of tolterodine perorally through a 2 mg tablet in human patients.

Description of the Invention

The present invention involves the use of antimuscarinic agents to treat urinary disorders, such as unstable or overactive urinary bladder.

Overactive urinary bladder encompasses various urinary disorders, including overactive urinary bladder detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency and LUTS (Lower Urinary Tract Symptoms giving obstructive urinary symptoms such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain

to urinate at an acceptable rate or irritate symptoms such as frequency an/ or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

The method of the present invention is used to treat mammals, including man. It is preferred that the mammal is a human.

Upon traditional tablet administration of antimuscarinic agents to treat urinary disorders, the plasma concentration thereof increases rather slowly, peaking after 1-2 hours. The antimuscarinic agents are often metabolized by the liver following oral dosing. According to the present invention, administration of antimuscarinic agents to patients for treatment of urinary disorders can advantageously be performed via inhalation or insufflation. Thereby, the antimuscarinic agents instantly gain access to the systemic circulation and can affect target tissues, such as the smooth musculature surrounding the urinary tract.

The compositions according to the invention can be made up in solid or liquid form, such as powders, sterile solutions, suspensions or emulsions, and the like.

The antimuscarinic agents of the present invention are administered by inhalation or insufflation. The

inhalation or insufflation is preferably by either an aerosol or a powder.

The method and the antimuscarinic agents and compositions of the present invention are useful for the treatment of unstable or overactive urinary bladder, e.g. urinary incontinence.

The dosage of the specific antimuscarinic agent will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kg of body weight, administered singly or multiply in doses e.g. from about 0.05 mg to about 200 mg each. A clinically effective amount of antimuscarinic agents is from about 0.05 mg to about 12 mg. It is preferred that the effective amount is from about 0.1 to about 6 mg; it is more preferred that the effective amount is from about 0.2 to about 5 mg.

The dosage form for inhalation can be an aerosol. The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the antimuscarinic agents may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many aerosols for treating asthma.

Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When the dosage form is a powder, the antimuscarinic agent can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the antimuscarinic agent is compounded such that the total amount of powder delivered delivers an "effective amount" of the agent. The actual concentration of the agent may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the agent.

The carriers may be of any inert material, organic or inorganic, suitable for administration via inhalation or insufflation, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, and the like.

Various devices are on the market for administering powders for inhalation for asthma, and these devices are suitable for administering the antimuscarinic agents of the present invention.

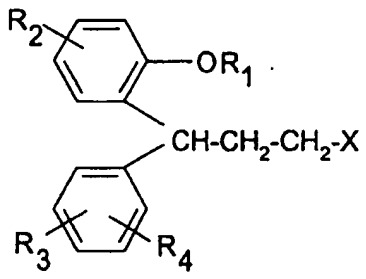
Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds that are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the following acids: tartaric, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, citric, methanesulfonic,

CH_3-$(CH_2)_n$-COOH where n is 0 through 4, HOOC-$(CH_2)_n$-COOH, where n is as defined above, HOOC-CH=CH-COOH, ϕ-COOH. For other acceptable salts, see Int. J. Pharm., 33: 201-217 (1986).

An exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the arylcycloalkane carboxylic esters disclosed in US-6,124,354 (the entire disclosures of which are incorporated by reference herein).

An exemplary specific antimuscarinic agent is 2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as metabolites, prodrug forms and pharmaceutically acceptable salts thereof.

Another exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-5,686,464 (the entire disclosures of which are incorporated by reference herein) and having the general formula:



wherein R_1 signifies hydrogen or methyl; R_2, R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group -NR_5,R_6, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be the same or different, especially C_{1-6}-alkyl or

adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R_5 and R_6 may form a ring together with the amine nitrogen, preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

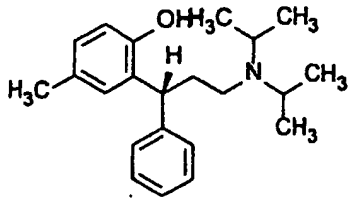
Exemplary specific compounds include tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, solvates, prodrug forms and pharmaceutically acceptable salts thereof.

Useful analogues to the above compounds are disclosed in WO 98/43942 (the full disclosure of which is incorporated by reference herein).

Specifically, the compositions according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

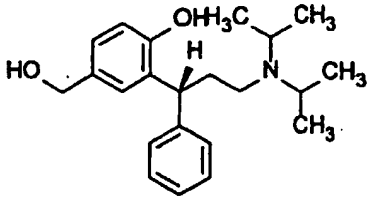
Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as (R)-N,N-

diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



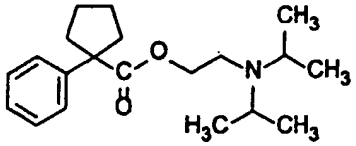
(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:



(R)-stereoisomer

2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, refers to a compound of the formula:



"Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of antimuscarinic agents include, but are not limited to, tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, and ipratropium.

Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-

butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha,alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

"Physiological saline" generally refers to a 0.9% aqueous sodium chloride solution.

"Pharmaceutically acceptable" refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Analogously, "inhalably acceptable" and "insufflably acceptable", respectively, refer to properties and/or substance which are pharmaceutically acceptable and also suitable for use via inhalation and insufflation, respectively.

Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various antimuscarinic agent and/or perform the various methods of the invention and are to be construed as merely illustrative, and not limitations of the preceding

disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Example 1. Pharmacokinetic comparison of systemic and local (aerosol) administration, respectively, of tolterodine

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Tolterodine L-tartrate, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-tartrate, for intraperitoneal administration was prepared in sterile 0.9% NaCl.

Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at a concentration of 1.0 mg/ml.

Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols of tolterodine for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Thus, mice received tolterodine either by aerosol generated from a 1 mg/ml solution for five minutes or by intraperitoneal (i.p.) injection at a dose of 3 mg/kg. Blood samples were taken via cardiac puncture under isoflurane anesthesia at 5, 15, 30, 60, 120, and 240 minutes after i.p. treatment and at 2.5, 5, 15, 30, 60, and 120 minutes after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels for tolterodine were determined by ESI-LC/MS/MS using a PE SCIEX API 3000 mass spectrometer in positive ion mode. Chromatographically, the analyte and internal standard were resolved on a Zorbax ACE Phenyl column(2.1 x 50mm) using a gradient elution. The total analysis time was 4 minutes with a limit of quantitation of 100pg/mL.

Plasma concentrations of tolterodine following 3 mg/kg i.p. injection and following 1 mg/ml aerosol exposure (inhalation) are summarized in Figure 1.

Example 2. Aerosol administration of different amounts of tolterodine

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml.

As described in Example 1, mice were exposed to aerosols of tolterodine generated from either 0.1, 0.5, or 1.0 mg/ml solutions. The duration of aerosol treatment was five minutes. Blood samples were collected via cardiac puncture at 2.5, 5, 15, 30, 60, and 120 minutes following the end of the drug nebulization period.

The samples from were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted and plasma levels for tolterodine were determined as described in Example 1.

Figure 2 shows plasma concentrations of tolterodine L-tartrate following inhalation of nebulized solutions at 0.1, 0.5, or 1.0 mg/mL. Plasma levels for the 0.1 mg/mL concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation.

Example 3. Comparative pharmacokinetic study of oral administration of tolterodine

This example illustrates the systemic distribution in man of perorally administrated prior art tolterodine tablets.

In 30 human patients with overactive bladder, the pharmacokinetic effects were determined of a film-coated tablet containing 2 mg of tolterodine L-tartrate. Serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) were measured over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6 and 9 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Figure 3 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM for the administration of a 2 mg tablet.

It is apparent that the patterns of blood concentrations of tolterodine and its active metabolite are altered upon aerosol administration thereof (examples 1 and 2, fig 1 and 2), when compared to prior art oral

administration (example 3, fig 3). Aerosol administration (fig 1 and 2) produces within a few minutes a distinct and instant rise in tolterodine plasma concentration, similar in pattern to what is seen upon intraperitoneal injection (fig 1). In contrast, oral administration (fig 3) results in slower uptake of tolterodine into the circulation, wherein a maximum blood concentration is reached in the range of one hour, and a concomitant prolonged presence of tolterodine in the circulation.

Claims

1. A method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

2. A method according to claim 1, wherein said disorder is unstable or overactive urinary bladder.

3. A method according to claim 1, wherein said disorder is urinary incontinence.

4. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol formulation.

5. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.

6. A method according to any one of claims 1-5, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

7. A method according to claim 6, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

8. A method according to claim 7, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

9. A method according to claim 8, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

10. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

11. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

12. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

13. A pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

14. A composition according to claim 13, wherein said disorder is unstable or overactive urinary bladder.

15. A composition according to claim 13, wherein said disorder is urinary incontinence.

16. A composition according to claim 13, which is an aerosol formulation.

17. A composition according to claim 13, which is a powder formulation.

18. A composition according to any one of claims 13-17, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

19. A composition according to claim 18, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-

(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

20. A composition according to claim 19, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

21. A composition according to claim 20, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

22. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.05 mg to about 12 mg.

23. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.1 to about 6 mg.

24. A composition according to claim 13, wherein said antimuscarinic agent is present in an amount of from about 0.2 to about 5 mg.

25. Use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

26. Use according to claim 25, wherein said disorder is unstable or overactive urinary bladder.

27. Use according to claim 25, wherein said disorder is urinary incontinence.

28. Use according to claim 25, wherein said medicament is an aerosol formulation.

29. Use according to claim 25, wherein said medicament is a powder formulation.

30. Use according to any one of claims 25-29, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic

esters, and inhalably or insufflably acceptable salts thereof.

31. Use according to claim 30, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

32. Use according to claim 31, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

33. Use according to claim 32, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

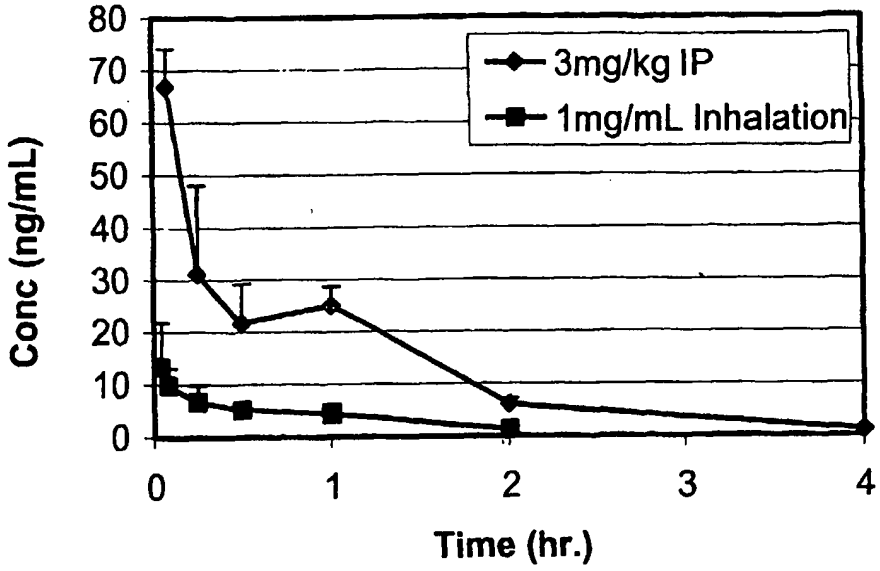


FIGURE 1

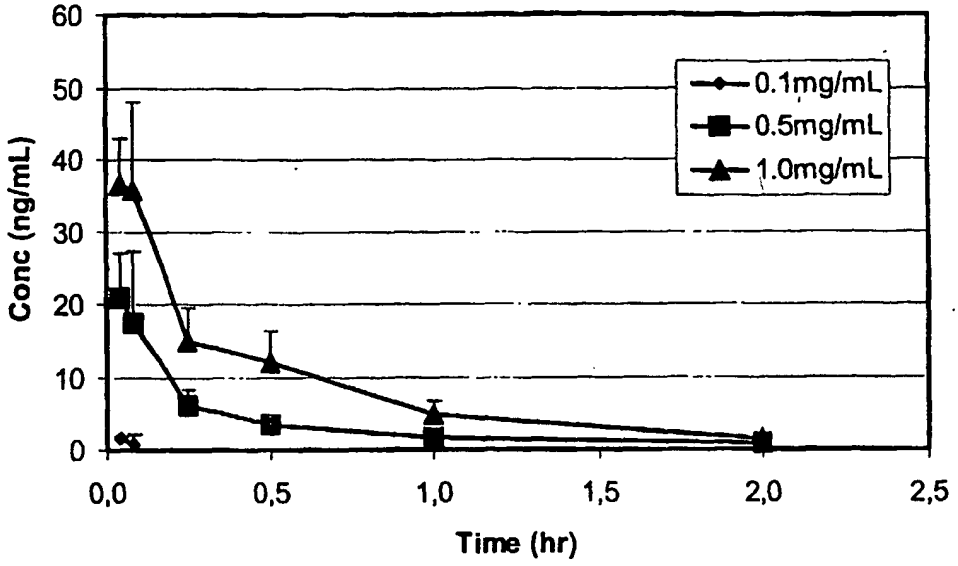


FIGURE 2

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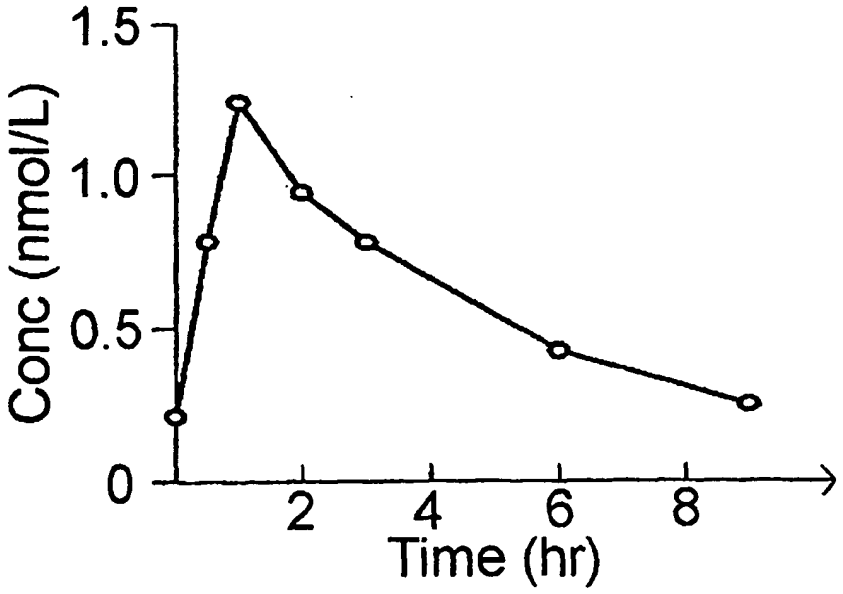

FIGURE 3

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIMUSCARINIC AEROSOL

(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a. treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

WO 2003/039464 A3

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/US 02/35335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/137 A61K31/216 A61K9/12 A61P13/00
A61P13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 002059 A (BRIDGE PHARMA INC) 9 January 2003 (2003-01-09) abstract page 5, last paragraph; claims 1-15	1-6, 10-18, 22-30
P,X	WO 02 17907 A (SHERRATT AMANDA J ;THERAMAX INC (US); HOUDI ABDULGHANI A (US)) 7 March 2002 (2002-03-07) the whole document	1-5, 10-17, 22-29
P,X	WO 02 34245 A (SUNDQUIST STAFFAN ;PHARMACIA AB (SE); GILLBERG PER GORAN (SE); UPJ) 2 May 2002 (2002-05-02) the whole document	13-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2003	14. 11. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int I Application No
PCT/US 02/35335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03067 A (ABERG GUNNAR) 29 January 1998 (1998-01-29) abstract page 4, paragraph 2; claims 1,2,4,6; examples	1-33
X	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application abstract page 6, line 36 - page 7, line 3 page 7, line 24 - line 28; claims; examples	1-33
X	WO 96 23492 A (SEPRACOR INC) 8 August 1996 (1996-08-08) abstract; claims 1-3,7,8; examples	1-5, 10-17, 22-29
X	US 5 736 577 A (MCCULLOUGH JOHN R ET AL) 7 April 1998 (1998-04-07) abstract column 2, line 55 - line 59 column 3, line 48 - line 52; claims 1,4; examples	1-5, 10-17, 22-29
X	"MARTINDALE, The complete drug reference" 2000, PHARMACEUTICAL PRESS , XP002246330 page 453 - page 454 page 754 - page 755 page 757	13-17, 22-24
A	EP 0 325 571 A (KABIVITRUM AB) 26 July 1989 (1989-07-26) cited in the application abstract page 6, line 59 - line 63; claims; example 22	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.....ational application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 10-19, 22-31 (all partially), 8, 9, 20, 21, 32, 33

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claims 1-5,10-17,22-29 relate to a compound defined by reference to a desirable characteristic or property, namely "antimuscarinic agent".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 1-6,13-18,25-30 relate to an extremely large number of possible compounds (in terms of 3,3-diphenylpropylamines, arylcycloalkane carboxylic esters, prodrug). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Again, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds tolterodine and hydroxytolterodine, with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7(partially),8,9,10-19(partially),20, 21,22-31(partially),32,33

Use of the antimuscarinic agents tolterodine and hydroxytolterodine for treating urinary disorders by inhalation or insufflation and composition thereof

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2. claims: 1-7(partailly),10-19(partially),22-31(partially)

Use of the antimuscarinic agent 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate for treating urinary disorders by inhalation or insufflation and composition thereof

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Inte al Application No
PCT/US 02/35335

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Inter[illegible]al Application No
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

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(54) Title: MULTI-STAGE ORAL DRUG CONTROLLED-RELEASE SYSTEM

(57) Abstract: The present invention relates to, as a novel oral drug delivery system for control of drug release, a preparation for maintaining drug concentration in blood at a certain level for a prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation.

MULTI-STAGE ORAL DRUG CONTROLLED-RELEASE SYSTEM

Technical Field

The present invention relates to, as a novel oral drug delivery system for controlling drug release, a preparation for maintaining drug concentration in blood at a certain level for prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation.

Background Art

Administration forms capable of controlling drug release become an important part of medication in terms of improved treatment effect, reduction of side effects and patient's convenience. Such controlled-release of drug is accomplished through designing of a system comprising the drug. Controlled-release of drug brings many therapeutic advantages, and the most important point is that blood level of drug can be maintained for long time while minimizing fluctuation of the blood level. Accordingly, allowing drug to be released at a constant rate from a preparation is the most important aspect in controlled-release preparation, and in particular, an amount of drug equivalent to that eliminated from the body should be released from the preparation and continuously absorbed while passing through the gastrointestinal tract.

Controlled-release preparations developed so far can be divided into three types, i.e. a type in which drug-containing particles (granules) are coated, matrix type mainly based on polymers, and a type based on osmotic pressure, and among them, the matrix form tablet has been interested greatly as a drug delivery system for the advantage of easy manufacture. When compared with tablets, because of the size and resultant increase of surface area, granules lead to relatively fast disintegration, resulting

in the disadvantage of a short drug-release time in a body.

Most matrix preparations release a drug via diffusion, and regarding with the matrix preparations, various techniques such as introducing water-insoluble coating layer on matrix particles in which drug is dispersed have been developed. In case components of coating layer and the matrix are insoluble in body fluid, diffusion of drug is controlled by the components of coating layer or matrix. Drug release from such preparation occurs by concentration gradient of drug introduced by water penetrated to the preparation. Such type of release shows a tendency of decline in the release rate at the last stage due to the gradual reduction of concentration gradient and the gradual increase of diffusion distance. Accordingly, release rate of drug cannot be maintained at a constant level but gradually reduces as a function of time, finally failing to maintain constant blood level of drug.

Such simple matrix tablets just extend the period of drug release, and exhibit inherent limit of releasing drug by first order kinetics or at a rate of $(\text{time})^{0.5}$. To maintain constant release rate, attempts to modify the previous matrix formulations have been made. Representative methods are to reduce initial drug release rate by introduction of a coating layer, to induce zero-order release rate by morphological approach to preparation, and to combine said two methods. Another approach is method of maintaining constant release rate by allowing diffusion distance to be reduced as a function of time through using erodible and swelling polymer as a main component of matrix.

Majority of the complements to the matrix preparation via coating were attempted for special object besides the control of release rate, e.g. enteric coated tablet or delayed release of drug in colon. As the best example of morphological approach to preparation, a method of regulating release area by introducing hydrophilic or

hydrophobic layer on both sides of drug-containing layer and a method of exposing constant area of the coated tablet can be enumerated.

Matrix formulation mainly consists of a drug and a biocompatible polymer, and in particular, in controlled-release preparation, polymer acts a very important role. Polymer matrix with the characteristic of swelling and erosion consists of swelling layer, diffusion layer and erosion layer, and has the advantage that drug release rate can be regulated at a fixed level based on the moving rates of swelling layer and erosion layer. However, also in case of using erosive polymer, release area deceases with time and this leads to typical matrix release mechanism pattern where release rate decreases with reduction of release area. To correct such drug release pattern, coating layer and a factor capable of controlling swelling were introduced. USP 6,156,343 retarded swelling and initial release by use of polyvinyl alcohol as material for matrix core, and by addition of a salt and introduction of a coating layer.

However, besides the simple erodible polymeric matrix system, non-erodible preparation with coating layer comprising water-insoluble polymer such as lacquer is still defective for time-dependent reduction of drug release, and osmotic preparation is disadvantageous for complicacy of the system and cost problem.

To overcome the declination of drug release with time, DE 1,767,765 developed multi-layer tablets, layers with different concentration of drug, and DE 2,651,176 designed a tablet in which drug concentration can increase from the outer layer towards the center. However, like osmotic preparation, the multi-layer tablet also has some disadvantages, necessity for special facility and complicate manufacture.

USP 4,252,786 designed a preparation in which the core of water-insoluble swelling polymer swells with penetration of water to lead to burst of coating layer.

Such pulsitile drug release is desirable for improving bioavailability of a drug whose first pass effect can be saturated, and it was revealed that drug release from the preparation is less sensitive to pH value of GI tract. Such preparation can freely control the delay of initial drug release, yet, drug release after the burst of the coating layer, still, depends on concentration gradient of drug.

USP 4,610,870 (Jain *et al.*) disclosed a coated tablet showing zero-order release rate. The core of this tablet includes hydroxypropylmethylcellulose and/or methylcellulose, one or more non-swellable binders and/or wax binders, one or more inert fillers or excipients, and one or more lubricant.

USP 4,252,786 by Weiss *et al.* resolved the rapid initial-release problem of swelling and erodible formulation by coating the swelling matrix core with a hydrophobic film coating layer capable of burst. Drug release in this preparation occurs via diffusion through initial non-damaged coating layer, and core expands by continuous penetration of external fluid, leading to burst of the coating layer. Thereafter, the swelling matrix core controls the drug release. Overall drug release is continuous based on such control of initial release, and zero-order release can be achieved.

Though said two patents resolved the problem of non-linear drug release that can occur in swelling and erodible matrix tablet by introducing a coating layer, it is still only simple coated tablet, therefore has failed in overcoming the feature and basic limitations of swelling and erodible matrix. Further, in case of a drug with high water-solubility, it is not effective for prolonged release over 24 hr.

USP Nos. 4,309,404 and 4,248,857 (DeNeale *et al.*) used

carboxypolymethylene as substance for core and introduced seal coating and sugar coating thereon, and USP No. 4,309,405 (Guley *et al.*) disclosed the similar formulation with the above one, using a combination of hydroxypropylmethylcellulose or hydroxypropylcellulose and hydrophobic polymer as core substance. These two formulations demonstrated zero-order release pattern over 12 hr, yet only after rapid initial drug release for 1 hr.

USP No. 4,610,870 discloses a coated tablet showing zero-order release pattern over 8 to 12 hr, and the coating layer of this tablet inhibits the rapid initial release while being gradually disappeared by swelling of the core layer, and then, drug is released with erosion of the core.

USP No. 5,464,633 introduced compressed layer instead of coating layer to swelling and erodible core matrix tablet in order to modify drug release rate, thereby preventing rapid initial drug release, and at the same time, endowed sustained release effect over prolonged time. In case of such multi-layer tablet, to remove inconvenience of coating for coated tablet, compressed layer was introduced, yet, for formation of compressed layered tablet, special facility and complicate calculation of release area were necessary.

USP No. 6,083,532 compensated for pH dependent behavior of drug solubility by using a combination of pH dependent substance and pH-independent polymer as a constituent of core matrix. Such release-modifying attempts were to make the release uninfluenced by individual patient's physiological condition, and applied as means for maximizing drug action. Such preparations can be applied to only specific group of drugs with specific pH-dependency, and as external fluid penetrates continuously into inside of the matrix, it sensitively reacts to pH within the gastrointestinal tract, thus it is difficult to expect continuously steady drug release.

USP No. 4,610,870 used a mixture of hydroxypropylmethylcellulose and methylcellulose as a gel-forming substance, and introduced a coating layer consisting of hydrophilic and hydrophobic materials on the core tablet. Based on this attempt, a preparation was designed to release procaine hydrochloride by zero-order over 8 to 12 hr.

USP No. 6,068,859 discloses controlled-release preparation of azithromycin where, in order to control time-dependent release of drug, the drug was dispersed and embedded in core matrix comprising four kinds of hydro-colloidal gel-forming substance and drug release was induced by erosion of the matrix, and when needed, a coating layer was introduced. As another method, a mixture of coated particles and particles without coating layer was introduced into a single capsule or tablet to allow drug to be released via release channel formed through the uncoated particles. Such preparations were attempted to achieve a comprehensive continuousness by combining each portions with different characteristics such as multi-particulate system, yet control on each part and mixing ratio thereof is necessary, so large amount of time and effort is required.

WO 99/47128 relates to tablet or capsule as biphasic sustained release delivery system, where particles comprising hydrophilic drug and hydrophobic polymer are dispersed in hydrophilic polymer. This system is applied to drugs with high water-solubility, such as metformin hydrochloride, to lead to increased release time and increased transit time in upper gastrointestinal tract by swelling of the preparation. Though the sustained release is effectively accomplished by controlling drug diffusion via adequate application of discontinuous phase of hydrophilic and hydrophobic substance, still, depends on concentration gradient. Therefore, it shows disadvantage of dumping effect due to rapid initial release and time-dependent reduction of release rate.

Therefore, it exhibits sustained release effect for about 10 hr in case of drug with high water-solubility, yet represents typical release profile for a matrix tablet, and thus not effective in terms of long term drug release for more than 24 hr and release rate control.

The conventional techniques as described above experienced difficulty in releasing drug at constant rate for prolonged time due to substantial problems such as time-dependent reduction of drug release area and increase of diffusion distance. In case of preparation based on osmotic pressure, zero-order release can be induced, but it has problem of complicated manufacturing process and high manufacturing cost.

The present invention makes it the object to provide an oral drug controlled-release preparation with minimized solubility-limit for drug to apply and improved stability, which can release drug at a constant rate for a long time without the disadvantages such as complicate manufacturing process and high manufacturing cost as in osmotic preparation or substantial problems such as time-dependent reduction of drug release area and increase of diffusion distance

Disclosure of the Invention

The present invention relates to, as a novel oral drug delivery system for control of drug release, a preparation for maintaining drug concentration in blood at a certain level for a prolonged time by allowing the drug to be released by a constant rate through stepwise control of drug release upon the administration of the preparation. More specifically, the present invention relates to controlled-release oral preparation characterized by stepwise release of granules from matrix and of drug from the granules, comprising

(1) granules comprising a drug and a carrier material in size of 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of a drug with water-solubility of 1 mg/ml or more, while hydrophilic material in case of a drug with water-solubility of less than 1 mg/ml;

(2) a matrix in which said granules are embedded, comprising swelling and erodible polymer(s) and swelling-regulating material(s); and

(3) a release-modifying layer comprising hydrophobic release-modifying polymer, hydrophilic release-modifying polymer, pH-dependent release-modifying polymer or a mixture thereof.

In general, the term "very soluble" is applied to what has water-solubility of 1 mg/ml or more and there is no upper limit of the solubility. The preparation in the present invention can be applied to any drug whose water-solubility is 1 mg/ml or more, accordingly, can also be applied to a drug with water-solubility of about 1 g/ml.

The preparation of the present invention is also applied to a drug with water-solubility of less than 1 mg/ml besides "very soluble" drug and there is no lower limit of the solubility. The preparation of the present invention can be applied to any drug with water-solubility of less than 1 mg/ml, accordingly, can be applied to a drug whose water-solubility is about 0.1 ng/ml.

It is preferred for the preparation of the present invention that 50 to 100% of the drug is present in granules, and the remaining exists within the erodible and swelling matrix or the release-modifying layer, or within the matrix and release-modifying layer in directly dispersed form.

The coated swelling-matrix oral preparation for control of drug release, according to the present invention, consists of three components: (1) Granules containing a drug; (2) swelling and erodible matrix where the drug-containing granules are embedded; and (3) a coating layer surrounding the matrix. Considering the drug release mechanism, coating layer provides initial lag-time for a certain amount of time. This is for enteric preparation or for release at specific site in the body. Further, coating layer functions in inhibiting dumping effect of drug release and in raising drug stability under storage. When said controlled-release preparation is exposed in the body fluid, coating layer disappears with swelling of inner matrix after the certain amount of time, leading to active swelling and erosion of the matrix. Swelling and erosion of the matrix leads to controlled-release of granules embedded in matrix and then drug is released in controlled way from the granules. In case of conventional swelling matrix system, direct release of drug from inner matrix leads to tendency of time-dependent decrease of drug release rate, while in case of the system according to the present invention, drug within the granules is directly released into matrix, and at the same time, drug-containing granules are continuously released and drug is released from the granules, i.e. multi-stage controlled-release, accordingly, drug release area increases with time due to cumulated granules to compensate the reduction of release rate according to reduction of surface area of erodible matrix itself, ultimately leading to drug release at constant rate.

The first constitution of the preparation according to the present invention is granules comprising a drug and a carrier material, wherein the size of said granules is 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of drug with water-solubility of 1 mg/ml or more, and hydrophilic material in case of drug with water-

solubility of less than 1 mg/ml.

In the preparation of the present invention, it is preferred that in case drug has a water-solubility within range from 1 mg/ml to 100 mg/ml, the drug-containing granules are prepared by wet granulation, and in case the drug has water-solubility of 100 mg/ml or more, the drug-containing granules are prepared into granules by dispersing the drug in hydrophobic fusible materials forming the granules.

Additionally, when water-solubility of the drug is less than 1 mg/ml, it is preferred to prepare the drug-containing granules according to solid dispersion method.

In case of drug with water-solubility of 1 mg/ml or more, it is preferred for said hydrophobic material forming the granules to be at least one selected from the group consisting of fatty acids, fatty acid esters, fatty acid alcohols, fatty acid mono-, di-, tri-glycerides, waxes, hydrogenated castor oil, hydrogenated vegetable oil and as like. Examples of the fatty acid alcohols include cetostearyl alcohol, stearyl alcohol, lauryl alcohol, myristyl alcohol and as like. Examples of the fatty acid esters include glyceryl monostearate, glycerol monooleate, acetylated monoglyceride, tristearin, tripalmitin, cetyl ester wax, glyceryl palmitostearate, glyceryl behanate (Compritol 888 ATO™) and as like. Examples of the waxes include beeswax, carnauba wax, glyco wax, castor wax and as like.

In case of drug with water-solubility of less than 1 mg/ml, for the preparation of the present invention, it is preferable that said hydrophilic carrier material forming granules is at least one selected from the group consisting of polyalkylene glycol and carboxyvinyl hydrophilic polymer. As specific example, polyethyleneglycol with

molecular weight of 1,000-6,000, carbomer (Carbopol™), calcium carboxymethylcellulose and sodium carboxymethylcellulose can be enumerated.

The granules of the preparation according to the present invention can further comprise other additives and excipients. As example, lactose, starch, mannitol, saccharose, glucose, sorbitol, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, microcrystalline cellulose (Avicel™), gelatin, polyvinylpyrrolidone and salt can be enumerated. The granules can contain at least one of the above additives. The granules can further contain, if necessary, cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, which accelerates disintegration of granules, and to correct pH dependence of drug, can contain inorganic acid and its conjugate base, or organic acid (such as citric acid and tartaric acid) and its conjugate base. The granules prepared as described above are the part that finally controls release and absorption of drug. In case of hydrophilic drugs, the control is achieved by diffusion through hydrophobic substance forming the granules, while in hydrophobic drugs, hydrophilic substance forming the granules, hydration environment established around the granules and increased surface area improve wettability of drug to increase the water-solubility thereof.

The second constitution of the preparation according to the present invention is matrix having said granule embedded therein, which comprising swelling and erodible polymer(s) and swelling-regulating material(s).

As the swelling and erodible polymer forming the matrix, for the formation of hydrogel matrix, at least one selected from the group consisting of

hydroxyalkylcellulose, hydroxypropylalkylcellulose, polyalkylene oxide, sodium alginate, povidone, polyvinyl alcohol and sodium carboxymethylcellulose can be used. In particular, it is preferred to use at least one selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyethylene oxide, sodium alginate, povidone polyvinyl alcohol and sodium carboxymethyl cellulose.

In addition, the matrix can further include adjuvant for formation of the swelling and erodible matrix, and at least one selected from the group consisting of cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, lactose, starch, mannitol, saccharose, glucose, sorbitol, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, microcrystalline cellulose (Avicel™), gelatin, polyvinylpyrrolidone, magnesium stearate, stearic acid, sodium stearate, talc, sodium benzoate, boric acid and colloidal silica, can be used. Also, the matrix can contain a portion of drug to be contained in granules.

Swelling-regulating material among said matrix components is used to control the degree and velocity of swelling of the polymer, and as the swelling-regulating material, cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone, or a mixture thereof can be used. The swelling-regulating material is preferred to be used in a content of 1 to 10% by weight to the total weight of matrix. The swelling and erodible polymer forming the core matrix provides, via swelling, hydration environment around the granules dispersed within the matrix. In particular, it acts a role of raising drug solubility in case of granules comprising hydrophobic drug. Further, it carries out function, secondary drug release control, by controlling the release of granules from the surface by erosion.

The third constitution of the preparation according to the present invention is release-modifying layer, and comprises at least one selected from the group consisting of hydrophobic release-modifying polymer, hydrophilic release-modifying polymer and pH-dependent release-modifying polymer.

In said release-modifying layer, the term "modifying" means that drug release from the preparation is again controlled by this layer, that is, release-modifying layer.

Hydrophobic release-modifying polymer as adequate material for forming the coating layer includes ethylcellulose, shellac and ammonio methacrylate copolymer (Eudragit RS™ or Eudragit RL™) and at least one of them can be used.

As adequate material for forming the coating layer, hydrophilic release-modifying polymer can be selected from the group consisting of hydroxyalkylcellulose and hydoxypropylalkylcellulose and at least one of them can be used, and preferably, selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxypentylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose and hydroxypropylpentylcellulose.

As material suitable for the formation of the coating layer, pH-dependent release-modifying polymer includes generally used enteric polymer. Specifically, it is possible to enumerate as follows: hydroxyalkylcellulose phthalate, hydroxyalkylmethylcellulose phthalate, cellulose acetyl phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate and anionic

copolymer of methacrylic acid and methyl or ethyl methacrylate. At least one selected from the group consisting of them can be used. As example for the anionic copolymer of methacrylic acid and methyl or ethyl methacrylate, Eudragit L and S can be enumerated.

Said release modifying layer can further includes plasticizer and, for example, it can be selected from the group consisting of castor oil, hydrogenated castor oil, fatty acid, substituted triglycerides and glyceride, polyethylene glycol of molecular weight within range of 300 to 50,000 and its derivatives. Such release modifying layer, i.e. coating layer, acts a role of primary drug release control and functions in modifying zero-order release rate of the matrix core. Using of pH dependent or hydrophobic polymer coating enables target-oriented system. For the coating layer, hydrophobic, hydrophilic and pH dependent polymers are used individually or in a combination of them. Coating solution includes plasticizer in a ratio of 5 to 50% by weight of the coating substance.

It is preferred for said release modifying layer to be 1 to 20% by weight to total weight of matrix. For the preparation of coating solution, water or organic solvent is used and as suitable organic solvent, methanol, ethanol, isopropanol, acetone, chloroform, dichloromethane and a mixture thereof can be used.

The oral drug controlled-release system of the present invention comprises granules containing effective amount of drug, swelling and erodible polymer matrix in which the granules are embedded, and a coating layer surrounding the core matrix consisting of the granules and matrix. It is preferred that granules containing the drug

reach 50 to 80% by weight to total weight of the preparation.

In the preparation according to the present invention, examples of the applicable drug is as follows:

therapeutic agents for aconuresis of oxybutynin, tolterodine and therapeutically equivalent salts thereof;

calcium channel blockers of nifedipine, verapamil, isradipin, nilvadipin, flunarizine, nimodipine, diltiazem, nicardipine, nisoldipin, felodipin, amlodipin, cinarizin and pendilin and pharmaceutically acceptable derivatives thereof;

beta-adrenergic antagonists of propranolol, metoprolol and pharmaceutically acceptable derivatives thereof;

angiotensin-converting enzyme inhibitors of captopril, enalapril, ramipril, fosinopril, altiopril, benazepril, libenzapril, alacepril, cilazapril, cilazaprilat, perindopril, zofedopril, lisinopril, imidapril, spirapril, rentiapril, delapril, alindapril, indalapril, quinalapril and therapeutically equivalent salts thereof;

non-steroidal anti-inflammatory agents of ketorolac, ketoprofen, benoxaprofen, caprofen, flubiprofen, fenoprofen, suprofen, fenbufen, ibuprofen, indoprofen, naproxen, miroprofen, oxaprozine, pranoprofen, pirprofen, thiaprofenic acid, fluprofen, alminoprofen, bucloxic acid, alclofenac acematacin, aspirin, indomethacin, ibufenac, isoxepac, profenac, fentiazac, clidanac, oxpinac, sulindac, tolmetin, zomepirac, zidometacin, tenclofenac, tiopinac, mefenamic acid, flufenamic acid, niflumic acid, meclofenamic acid, tolfenamic acid, diflufenisal, isoxicam, sudoxicam and therapeutically equivalent salts thereof;

therapeutic agents for respiratory disorders of theophylline, salbutamol, aminophylline, dextromethorphan, pseudoephedrine and therapeutically equivalent salts thereof;

analgesics of tramadol, acetaminophen, morphine, hydromorphone, oxycodone, propoxyphene and therapeutically equivalent salts thereof;

psychoneural drugs of fluoxetine, paroxetine, buspirone, bupropion, carmabazepine, carvidopa, levodopa, methylphenidate, trazodone, valproic acid, amitriptyline, carbamazepine, ergoloid, haloperidol, lorazepam and therapeutically equivalent salts thereof;

antibiotics of azithromycin dihydrate, cepha antibiotics, clarithromycin, doxycycline, nitrofurantonin and therapeutically equivalent salts thereof;

antihyperlipidemic agent of bezafibrate, fenofibrate, ethofibrate, lovastatin and therapeutically equivalent salts thereof;

antidiabetic agent of glyburide, glipizide, metformin and therapeutically equivalent salts thereof; and

cyclobenzaprin, favotidin, nizatidine, propafenone, clonazepam, hyoscyamine, diphenhydramine, olistat, doxazosin and therapeutically equivalent salts thereof.

It is preferable for the granules to be prepared by wet granulation, in case of water-soluble drug. For example, a drug, substance forming the granules as described above and at least one kind of additives are mixed and combined by adding binder solution comprising hydrophilic polymer and water or organic solvent such as denatured anhydrous ethanol as granulating fluid. Granulating fluid is added until wet mixture is formed and then the wet mixture is passed through 6~18 mesh sieve. This is dried in an oven at 24 to 60°C for 12 to 24 hr. The dried granules are screened with 10~24 mesh sieve.

In case a drug has water-solubility of 50 mg/ml or more, for effective release-

delay, drug particles can be covered with hydrophobic substance by melt-granulation. At a temperature of at least melting point of delivery system component, drug and other additives are mixed, dispersed and slowly cooled to obtain solid body of the delivery system, and granules are obtained by pulverization and screening.

In case of hydrophobic drug, it is preferable that drug, granule component described above and at least one additive are admixed, melted at melting point of the granule component to obtain solid dispersion. For example, granule-forming additives are added to the formed solid dispersion until granules are formed. The granules are screened through 6~18 mesh sieve, and then dried in an oven at 24 to 60°C for 12 to 24 hr. The dried granules are screened with 10~24 mesh sieve. Granules prepared as described above are mixed with swelling and erodible polymer and at least one additive forming matrix. Lubricant is added to the mixture and the final mixture is prepared into compressed tablet of core matrix without coating layer. Coating layer is formed by using hydrophobic polymer, hydrophilic polymer and enteric or pH dependent substance, individually or in a mixture. At least one polymer for the formation of coating layer and plasticizer is made ready in a form dispersed in water or organic solvent and then the dispersion solution is sprayed on the core matrix prepared as above. Coated tablet is finally dried in an oven at 40 to 50°C. For stability and color of preparation, seal coating can be conducted. In order to allow drug concentration to rapidly reach effective blood level, 1 to 20% of drug can be directly contained within the coating layer.

Drug release through the multi-stage controlled-release system according to the present invention is controlled via three steps.

At the first step, coating layer, i.e. release-modifying layer exhibits intentional release-delaying effect over a certain amount of time. In case of coating layer consisting of hydrophilic polymer alone, overall release profile is not influenced and release pattern of the core matrix itself is maintained, leading to maintenance of zero-order release profile over an 8 to 24 hr or more periods. In case hydrophilic or enteric polymer is used along with hydrophobic polymer, after release-delay over a certain amount of time is maintained, external fluid is penetrated through pores formed by dissolution of hydrophilic or enteric polymer and hydrophilic plasticizer and the penetrated fluid starts to swell the core matrix. Swelling pressure of the core matrix causes disappearing of coating layer and zero-order release of drug occurs. When coated with enteric polymer, below pH 4.0, there is no release, then at pH 4.0 or more, release starts with loss of the coating layer.

At the second step, swelling of the core matrix actively undergoes upon the disintegration and dissolution of the coating layer, and leads to establishment of hydration environment around the granules embedded in the matrix. As erosion of matrix component starts from the surface of the swelling matrix, granules are to be released by a constant rate.

It is preferred for the preparations of the present invention that, by erosion of the surface of matrix, 0 to 20% of total granules is released over 0 to 4 hr, 0 to 50% is released over 0 to 8 hr, 0 to 70% is released over 0 to 16hr, and 0 to 100% is released over 0 to 24 hr.

At the third step, finally, drug is released by diffusion through pores formed

within the granules and by osmotic pressure difference against the external fluid.

Drug release pattern of core matrix itself maintains zero-order release, and introducing of coating layer brings delay over a certain amount of time to lead to intentional appearance of biphasic zero-order release pattern. Release rate can be controlled in various ways by ratio of granules component forming the system and amount of granules, amount of swelling polymer and ratio of swelling matrix to granules, and ratio and amount of hydrophobic, hydrophilic or enteric polymer forming the coating layer.

The system prepared according to the present invention is oral multi-stage controlled-release system and suitable for designing oral drug delivery system taken once or twice a day which exhibits controlled-release for a long time and on specific target for the drug's therapeutic purpose. Drug is released from granules that are released from matrix by swelling and erosion, and cumulated released-granules allow surface area for drug release to be maintained at a constant level. Thus, this compensates the decrease of drug release rate according to reduction of surface area by erosion of matrix, leading to prolonged drug release at constant rate. Maintaining of zero-order release rate enables blood level of drug to be kept at a steady level for a long time.

Best Mode for Carrying Out the Invention

The Examples given below are just to explain the present invention and, in any case, they should not be regarded as limiting the scope of the present invention, and in view of the detailed description of invention and the patent claims, the Examples and

their equivalents are obvious to persons skilled in the art.

Examples 1~5. Preparations of core matrix tablet containing oxybutynin

Oxybutynin, glyceryl behanate, solubilizer, binder, release-regulating agent and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. The following Table 1 represents the ingredients of the core matrix tablet.

Table 1. Compositions of core matrix tablet containing oxybutynin

Ingredient (mg)	Example 1	Example 2	Example 3	Example 4	Example 5
Oxybutynin hydrochloride	5	5	5	5	5
Glyceryl behanate	10	10	20	15	15
Dibasic calcium phosphate dihydrate	35.9	45.9	55.9	56.85	28.425
Lactose	-	-	-	-	28.425
Sodium chloride	-	-	-	17.63	17.63
Sodium lauryl sulfate	0.1	0.1	0.1	0.15	0.15
Povidone	6	6	6	9	9
Cross-linked sodium carboxymethylcellulose	-	-	-	-	15
Hydroxypropylmethyl cellulose	40	30	20	45	30
Magnesium stearate	3	3	3	1.5	1.5
Total	100	100	100	150	150

Experimental Example 1. Dissolution test for the preparations of Examples 1~5

Release profile of core matrix tablet prepared in said Examples 1-5 was determined by USP dissolution test method under conditions of simulated intestinal fluid (fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and dissolution level according to time was measured. The result was represented by dissolution percentage as function of time in Table 2.

Table 2. Dissolution percentage (%)

Time (hr)	Example 1	Example 2	Example 3	Example 4	Example 5
0	0.00	0.00	0.00	0.00	0.00
1	11.03	14.47	10.51	4.78	15.27
2	10.74	18.56	15.51	10.29	32.75
3	13.53	20.30	14.81	16.01	41.93
4	14.18	25.22	20.77	20.00	48.53
6	17.07	31.54	28.14	30.65	58.80
8	24.04	40.52	37.91	38.86	62.73
10	29.81	48.68	45.35	46.23	68.64
12	36.70	58.42	43.76	53.48	72.06
24	68.74	84.54	72.98	91.73	93.01

Based on the dissolution test result for the controlled-release preparation of the present invention obtained in Examples 1-5, it was confirmed that various controlled-release patterns of oxybutynin could be obtained by the core matrix tablet itself, and the release rate could be controlled by regulating the content of swelling and erodible polymer and glyceryl behanate. Example 4 represents zero-order release pattern over 24 hr, and Example 5 shows that the release pattern can be affected by the content of swelling-regulating material contained in the matrix.

Examples 6 and 7. Preparations of core matrix tablet containing oxybutynin

Oxybutynin, glyceryl behanate, solubilizer, binder, release-regulating agent and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Polyethylene oxide, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. The following Table 3 represents the ingredients of the core matrix tablet.

Table 3. Compositions of core matrix tablet containing oxybutynin

Ingredient (mg)	Example 6	Example 7
Oxybutynin hydrochloride	5	5
Hydrogenated castor oil	5	15
Dibasic calcium phosphate dihydrate	65	55
Sodium chloride	17.85	17.85
Sodium lauryl sulfate	0.15	0.15
Povidone	9	9
Polyethylene oxide	45	45
Magnesium stearate	3	3
Total	150	150

Experimental Example 2. Dissolution test for the preparations of Examples 6 and 7

Release profiles of the core matrix tablets prepared in said Examples 6 and 7 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and dissolution level according to time was measured. The result was represented by dissolution percentage as function of time in Table 4.

Table 4. Dissolution percentage (%)

Time (hr)	Example 6	Example 7
0	0.00	0.00
1	5.57	3.11
2	10.26	4.98
3	10.75	6.44
4	15.67	8.75
6	24.20	14.86
8	60.99	49.38
18	67.38	59.29
20	67.72	62.02
24	71.30	66.00

Examples 8-10. Coating of core matrix tablet containing oxybutynin

The core matrix tablet prepared in said Example 2 was coated with a mixture of hydrophilic release-modifying polymer and hydrophobic release-modifying polymer, i.e. hydroxypropylmethylcellulose and ethylcellulose. Coating solution was prepared according to the composition given in Table 5. Spray coating was carried out in pan coater, and then the products were dried in oven at 40 to 50°C for 12 to 24 hr.

Table 5. Coating Solution Composition

Components (%)	Example 8	Example 9	Example 10
Hydroxypropylmethylcellulose	5.4	4.8	4.2
Ethylcellulose	0.6	1.2	1.8
Castor oil	0.7	0.7	0.7
Ethanol	46.7	46.7	46.7
Methylene chloride	46.7	46.7	46.7
Coating %*	3	3	3

*Coating degree to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 3. Dissolution test for the preparations of Examples 8~10

Release profiles of the coated core matrix tablets prepared in said Examples 8-

10 were determined by USP dissolution test apparatus under conditions of pH 4.0 solution, paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 6.

Table 6. Dissolution percentage (%)

Time (hr)	Example 8	Example 9	Example 10
0	0.00	0.00	0.00
1	6.16	6.07	3.74
2	11.53	10.67	7.07
3	17.28	16.01	10.59
4	24.66	19.82	13.69
6	34.47	27.63	20.04
8	45.13	34.60	27.23
10	54.51	41.98	31.46
12	63.67	50.11	37.56
24	100.72	85.25	69.06

The dissolution test results for the coated core matrix of Examples 8 to 10 reveal that drug release rate of core matrix showing zero-order release pattern can be regulated by relative content of hydrophobic release-modifying substance contained in the coating layer.

Examples 11 and 12. Coating of core matrix tablet containing oxybutynin

The core matrix tablets prepared by said Examples 4 and 5 were coated with a mixture of hydrophobic release-modifying polymer and pore-forming substance, i.e. ethylcellulose and polyethyleneglycol (MW 300). Coating solution was prepared according to the composition given in Table 7. Spray coating was carried out in pan coater, and then the products were dried in oven at 40 to 50°C for 12 to 24 hr.

Table7. Coating Solution Composition

Components (%)	Example 11	Example 12
Ethylcellulose	7.0	7.0
Polyethylene glycol (MW: 300)	2.8	2.8
Ethanol	90.2	90.2
Coating %*	1.0	1.0

*Degree of coating to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 4. Dissolution test for the preparations of Examples 11 and 12

Release profiles of the coated core matrix tablet prepared in said Examples 11 and 12 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 8.

Table 8. Dissolution percentage (%)

Time (hr)	Example 11	Example 12
0	0.00	0.00
1	0.00	4.67
2	1.68	17.61
3	3.45	19.41
4	5.89	27.70
6	10.55	34.38
18	35.79	64.76
20	41.92	72.18
22	49.87	79.45
24	55.24	99.32

The dissolution test result for the coated core matrix of Examples 11 and 12 demonstrates that the depth of coating and the content of hydrophilic release-modifying polymer, that is, pore-forming material can modify the drug release rate of core matrix

showing zero-order release pattern.

Examples 13~15. Coated core matrix tablet containing oxybutynin

Preparation process for matrix core is the same as in Examples 1-5. Example 13 includes within granules citric acid, substance for regulating pH-surrounding granules, instead of sodium chloride, and includes swelling-regulating material to control the swelling pressure and the swelling speed of matrix. In case of Examples 14 and 15, swelling-regulating material exists in both granules and matrix. As coating substance, shellac was used, and the compositions of the coating solution and the core matrix are represented in the following Table 9.

Table 9. Compositions of core matrix tablet containing oxybutynin and coating solution

	Ingredient (mg)	Example 13	Example 14	Example 15
Core Matrix	Oxybutynin hydrochloride	5	5	5
	Glyceryl behanate	15	15	15
	Dibasic calcium phosphate dihydrate	28.425	28.425	28.425
	Lactose	31.925	41.925	41.925
	Sodium chloride	-	17.35	17.35
	Citric acid	17.5	-	-
	Sodium lauryl sulfate	0.15	0.15	0.15
	Povidone	9	9	9
	Cross-linked sodium carboxymethylcellulose	1.5	1.65	1.65
	Hydroxypropylmethylcellulose	30	30	30
	Magnesium stearate	1.5	1.5	1.5
	Moisture*	q.s.	q.s.	q.s.
	Total	150	150	150
Coating solution	Shellac(OPAGLOSGS-2-0401)	50%	50%	50%
	Ethanol	50%	50%	50%
	Coating%+	5	1	5

*Removed during treatment process.

+ Degree of coating to the weight of uncoated core matrix tablet is represented by %.

Experimental Example 5. Dissolution test for the preparations of Examples 13 and 14

Release profiles of the coated core matrix tablets prepared in said Examples 13 and 14 were determined by USP dissolution test apparatus under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 10.

Table 10. Dissolution percentage (%)

Time (hr)	Example 13	Example 14
0	0.00	0.00
1	1.20	3.96
2	3.28	9.72
3	22.85	24.45
4	30.15	32.45
6	43.64	40.94
19	79.36	86.58
20	81.34	90.45
22	84.22	93.63
24	87.00	98.03

The dissolution test result for the coated core matrix tablets of Examples 13 and 14 shows that achieving release-delay effect over a certain amount of time by controlling depth of shellac coating leads to biphasic release pattern. The release-delay and the rapid drug release after the period can be induced by regulating the content of swelling-regulating material contained in the core matrix.

Experimental Example 6. Dissolution test for the preparations of Examples 13~15

Release profiles of the coated core matrix tablets prepared in said Examples 13

to 15 were determined by USP dissolution test method (paddle type II, 50 rpm/900 ml). According to the simulated GI method (Gastrointestinal method), the test was conducted in simulated stomach fluid (Fluid I, pH 1.2) for 2 hr and then under simulated intestinal fluid (Fluid II, pH 6.8), time-dependent dissolution level over 24 hr was measured. The result was represented by dissolution percentage as function of time in Table 11.

Table 11. Dissolution percentage (%)

Time (hr)	Example 13	Example 14	Example 15
0	0.00	0.00	0.00
0.5	1.97	10.29	4.78
1	7.02	24.50	10.03
1.5	15.34	33.90	20.96
2	20.54	44.03	28.13
3	28.87	51.67	41.58
4	35.30	55.25	40.00
6	46.86	62.19	47.18
18	73.23	89.89	85.36
20	76.85	92.43	85.02
22	81.44	94.67	86.37
24	83.50	96.41	91.26

Examples 16-18. Coated core matrix tablet containing oxybutynin

Preparation process of matrix core is the same as in Examples 1-5. Example 16 includes swelling-regulating material within granules and matrix to control swelling pressure and swelling speed of matrix. In case of Examples 17 and 18, the content of swelling and erodible polymer within the matrix was increased or reduced, respectively. As coating substance, a mixture of 1:1 ratio of enteric polymer, i. e. hydroxy-propylmethylcellulose phthalate, and shellac was used. Compositions of the coating solution and core matrix are represented in Table 12.

Table 12. Compositions of core matrix tablet containing oxybutynin and coating solution

	Ingredient (mg)	Example 16	Example 17	Example 18
Core Matrix	Oxybutynin hydrochloride	5	5	5
	Glyceryl behanate	15	15	15
	Dibasic calcium phosphate dihydrate	28.425	28.425	28.425
	Lactose	41.925	41.925	26.925
	Sodium chloride	17.35	17.35	17.35
	Citric acid	-	-	-
	Sodium lauryl sulfate	0.15	0.15	0.15
	Povidone	9	16.5	9
	Cross-linked sodium carboxymethylcellulose	1.65	1.65	1.65
	Hydroxypropylmethyl cellulose	30	22.5	45
	Magnesium stearate	1.5	1.5	1.5
	Moisture*	q.s.	q.s.	q.s.
	Total	150 mg	150 mg	150 mg
Coating solution	Shellac (OPAGLOS GS-2-0401)	2.68%	2.68%	2.68%
	Hydroxypropylmethyl cellulose phthalate	2.68%	2.68%	2.68%
	Methylene chloride	48.66%	48.66%	48.66%
	Ethanol	45.99%	45.99%	45.99%
	Coating%+	4	4	4

*Removed during treatment process.

+ Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 7. Dissolution test for the preparations of Examples 16~18

Release profiles of the coated core matrix tablets prepared in said Examples 16 to 18 were determined by USP dissolution test method (paddle type II, 50 rpm/900 ml), and according to the simulated GI method (Gastrointestinal method). The test was conducted in simulated stomach fluid (Fluid I, pH 1.2) for 2 hr and then under simulated intestinal fluid (Fluid II, pH 6.8), time-dependent dissolution level over 24 hr was measured. The result was represented by dissolution percentage as function of time in

Table 13.

Table 13. Dissolution percentage (%)

Time (hr)	Example 16	Example 17	Example 18
0	0.00	0.00	0.00
0.5	0.00	0.00	0.00
1	0.00	0.00	0.00
1.5	0.00	0.00	0.00
2	0.00	0.00	0.00
3	5.01	0.00	0.00
4	8.55	2.29	3.31
6	18.51	14.52	11.09
8	28.50	32.33	19.86
18	73.27	77.65	51.32
20	75.66	82.15	55.05
22	78.63	81.52	55.15
24	81.87	83.72	58.58

The dissolution test result for the coated core matrix of Examples 14 to 16 represents that pH-dependent release of drug could be corrected by introducing substance with pH dependency into the coating layer, and that drug release was inhibited during the stay in stomach for 2-3 hr and, thereafter, exhibited zero-order release pattern up to 24 hr.

Example 19. Coated core matrix tablet containing Ketorolac

Ketorolac tromethamine, glyceryl behanate, solubilizer, binder, release-regulating material and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. The granules thus formed were screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethyl cellulose, binders, swelling-regulating agent and diluents were added to the screened

granules, and then they were mixed for 10 min. Finally, lubricant was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. The following Table 14 represents the ingredients of the core matrix tablet and composition of the coating solution.

Table 14. Composition of the core matrix tablet and the coating solution

	Ingredient (mg)	Example 19
Core Matrix	Ketorolac tromethamine	10
	Glyceryl behanate	30
	Dibasic calcium phosphate dihydrate	39.35
	Sodium chloride	15
	Sodium lauryl sulfate	0.15
	Povidone	9
	Hydroxypropylmethylcellulose	45
	Magnesium stearate	1.5
	Moisture*	q.s.
	Total	150
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process.

+ Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 8. Dissolution test for the preparations of Example 19

Release profile of the coated core matrix tablet prepared in said Example 17 was determined by USP dissolution test method under condition of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage

as function of time in Table 15.

Table 15. Dissolution percentage (%)

Time (hr)	Example 19
0	0.00
1	20.61
2	33.43
3	44.80
4	54.33
6	70.26
8	83.40
12	96.17

Ketorolac was released from the coated core matrix tablets of Example 19 at a constant rate up to 12 hr, and the release rate could be regulated by the content of swelling material within the matrix and by the coating depth.

Example 20. Coated core matrix tablet containing enalapril maleate

Therapeutic composition containing enalapril maleate according to the present invention is prepared as follows. First, enalapril maleate, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. The

following Table 16 represents the ingredients of the core matrix tablet and composition of the coating solution.

Table 16. Compositions of core matrix tablet and coating solution

	Ingredient (mg)	Example 20
Core Matrix	Enalapril maleate	10
	Glyceryl behanate	30
	Dibasic calcium phosphate dihydrate	39.35
	Sodium chloride	15
	Sodium lauryl sulfate	0.15
	Povidone	9
	Hydroxypropylmethylcellulose	45
	Magnesium stearate	1.5
	Moisture*	q.s.
	Total	150
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process

+Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 9. Dissolution test for the preparations of Example 18

Release profile of the coated core matrix tablet prepared in said Example 18 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 17.

Table 17. Dissolution percentage (%)

Time (hr)	Example 18
0	0.00
1	20.61
2	33.43
3	44.80
4	54.33
6	70.26
8	83.40
12	96.17

Example 21. Coated core matrix tablet containing captopril

Therapeutic composition containing captopril according to the present invention is prepared as follows. First, captopril, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Thus prepared core matrix tablets were spray coated in pan coater and dried in oven at 40 to 50°C for 12 to 24 hr. Ingredients of the core matrix tablet and composition of the coating solution are shown in Table 18.

Table 18. Compositions of core matrix tablet and coating solution

	Ingredient (mg)	Example 21
Core Matrix	Captopril	25
	Glyceryl behanate	62.5
	Dibasic calcium phosphate dihydrate	5
	Povidone	5
	Hydroxypropylmethylcellulose	150
	Magnesium stearate	2.5
	Moisture*	q.s.
	Total	250
Coating solution	Hydroxypropylmethylcellulose	9.6%
	Ethyl cellulose	2.4%
	Methylene chloride	93.4%
	Ethanol	93.4%
	Castor oil	1.2%
	Coating%+	10

*Removed during treatment process

+Degree of coating to the weight of the uncoated core matrix tablet is represented by %.

Experimental Example 10. Dissolution test for the preparations of Example 21

Release profile of the coated core matrix tablet prepared in said Example 19 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 19.

Table 19. Dissolution percentage (%)

Time (hr)	Example 21
0	0.00
1	13.64
2	23.51
3	33.40
4	38.77
8	61.48
19	80.67
20	82.13
22	84.19
24	90.79

Example 22. Preparation of core matrix tablets containing diltiazem

Therapeutic composition containing diltiazem according to the present invention is prepared as follows. First, diltiazem hydrochloride, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Ingredients of the core matrix tablet are shown in Table 20.

Table 20. Compositions of core matrix tablet containing diltiazem

	Ingredient (mg)	Example 22
Core Matrix	Diltiazem hydrochloride	90
	Glyceryl behanate	40
	Dibasic calcium phosphate dihydrate	90
	Sodium chloride	45
	Sodium lauryl sulfate	1
	Povidone	10
	Hydroxypropylmethylcellulose	120
	Magnesium stearate	4
	Moisture*	q.s.
	Total	400

*Removed during treatment process

Experimental Example 11. Dissolution test for the preparations of Example 22

Release profile of the coated core matrix tablet prepared in said Example 22 was determined by USP dissolution test method under conditions of simulated intestinal fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 21.

Table 21. Dissolution percentage (%)

Time (hr)	Example 22
0	0.00
1	13.40
2	20.94
3	27.56
4	33.58
6	45.12
8	55.18
10	64.38
12	72.01
16	90.50
20	100.72

Example 23. Preparation of core matrix tablets containing theophylline

Therapeutic composition containing theophylline according to the present invention is prepared as follows. First, theophylline hydrochloride, glyceryl behanate, solubilizer, binder, release-regulating substance and inert diluents were mixed for 10 min at dry state. The mixture, after water was added, was granulated for 5 min. Granules thus formed was screened through 18-mesh sieve and dried in an oven at 24 to 40°C for 12 to 24 hr. The dried granules were screened with 20-mesh sieve. Hydroxypropylmethylcellulose, binders, swelling-regulating agent and diluents were added to the screened granules, and then they were mixed for 10 min. Finally, magnesium stearate was added to them, and then they were mixed for 5 min. The mixture was compressed to prepare tablets. Ingredients of the core matrix tablet are shown in Table 22.

Table 22. Composition of core matrix tablet containing theophylline

	Ingredient (mg)	Example 23
Core Matrix	Theophylline	200
	Glyceryl behanate	80
	Dibasic calcium phosphate dihydrate	380
	Sodium chloride	90
	Sodium lauryl sulfate	2
	Povidone	20
	Hydroxypropylmethylcellulose	120
	Magnesium stearate	8
	Moisture*	q.s.
	Total	900

*Removed during treatment process

Experimental Example 12. Dissolution test for the preparations of Example 23

Release profile of the coated core matrix tablet prepared in said Example 23 was determined by USP dissolution test method under conditions of simulated intestinal

fluid (Fluid II, pH 6.8), paddle type II and 50 rpm/900 ml, and time-dependent dissolution level was measured. The result was represented by dissolution percentage as function of time in Table 23.

Table 23. Dissolution percentage (%)

Time (hr)	Example 23
0	0.00
1	11.83
2	17.60
3	22.65
4	26.87
6	35.11
8	41.73
10	47.61
12	50.37
24	72.19

The present invention can provide a constant release rate over an 8 to 24 hr or more period by allowing drug to be released from granules released from matrix, as well as directly from inside of the matrix, and by regulating the release rate of the granules by the content of swelling-regulating material within the matrix. Further, the present invention minimized solubility-limit of drug by applying a suitable manufacturing method and components of the granules in consideration of water-solubility of drug.

Industrial Applicability

The present invention provides oral drug controlled-release preparation with sustained-release effect proper to the characteristics of drug action, as well as with improved stability, by inducing zero-order release through effectively allowing drug release area to be maintained at a fixed level and through introducing a release-modifying layer.

CLAIMS

1. A controlled-release oral preparation characterized in that release of granules from matrix and drug release from the granules are conducted in stepwise way, wherein the preparation comprises:

(1) granules comprising a drug and a carrier material in size of 0.1 ~ 1 mm, said carrier material is hydrophobic material in case of drug with water-solubility of 1 mg/ml or more and said carrier material is hydrophilic material in case of drug with water-solubility of less than 1 mg/ml;

(2) a matrix in which said granules are embedded, comprising swelling and erodible polymer and swelling-regulating material; and

(3) a release-modifying layer comprising hydrophobic release-modifying polymer, hydrophilic release-modifying polymer, pH-dependent release-modifying polymer or a mixture thereof.

2. The controlled-release oral preparation in Claim 1, wherein 50 to 100% of the drug is present within the granules, and the remaining drug exists within the matrix or the release-modifying layer, or within the matrix and the release-modifying layer in directly dispersed form.

3. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility within range from 1 mg/ml to 100 mg/ml, and the granules containing the drug is prepared by wet granulation.

4. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility of at least 100 mg/ml, and the granules containing the drug is prepared in

granular form by dispersing the drug in fusion of granules components.

5. The controlled-release oral preparation in Claim 1, wherein the drug has a water-solubility of less than 1 mg/ml, and the granules containing the drug is prepared by solid dispersion method.

6. The controlled-release oral preparation in Claim 1, wherein the hydrophobic material is at least one selected from the group consisting of fatty acids, fatty acid esters, fatty acid alcohols, fatty acid mono-, di-, tri-glycerides, waxes, hydrogenated castor oil and hydrogenated vegetable oil.

7. The controlled-release oral preparation in Claim 6, wherein the fatty acid alcohol is at least one selected from the group consisting of cetostearyl alcohol, stearyl alcohol, lauryl alcohol and myristyl alcohol; fatty acid ester is at least one selected from the group consisting of glyceryl monostearate, glycerol monooleate, acetylated monoglyceride, tristearin, tripalmitin, cetyl ester wax, glyceryl palmitostearate and glyceryl behanate; and wax is at least one selected from the group consisting of beeswax, carnauba wax, glyco wax and castor wax.

8. The controlled-release oral preparation in Claim 1, wherein the hydrophilic material is at least one selected from the group consisting of polyalkylene glycol and carboxyvinyl hydrophilic polymer, and the drug is solid-dispersed in said hydrophilic polymer.

9. The controlled-release oral preparation in Claim 1, wherein the swelling and erodible

polymer is at least one selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethylcellulose, polyethylene oxide, sodium alginate, povidone, polyvinyl alcohol and sodium carboxymethylcellulose.

10. The controlled-release oral preparation in Claim 1, wherein said swelling-regulating material is at least one selected from the group consisting of cross-linked sodium carboxymethylcellulose and cross-linked polyvinylpyrrolidone.

11. The controlled-release oral preparation in Claim 1, wherein said hydrophobic release-modifying polymer used for the formation of release-modifying layer, is at least one selected from the group consisting of ethylcellulose, shellac and ammonio methacrylate copolymer; said hydrophilic release-modifying polymer is at least one selected from the group consisting of hydroxyalkylcellulose and hydroxypropylalkylcellulose; and said pH-dependent release-modifying polymer is at least one selected from the group consisting of hydroxyalkylcellulose phthalate, hydroxyalkylmethylcellulose phthalate, cellulose acetyl phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate, and anionic copolymer of methacrylic acid with methyl or ethyl methacrylate.

12. The controlled-release oral preparation in Claim 1, wherein said release-modifying layer is 1 to 20% by weight to total weight of matrix, and the granules containing the drug reach 50 to 80% by weight to total weight of the preparation.

13. The controlled-release oral preparation in Claim 1, wherein the drug is selected from the following group:

therapeutic agents for aconuresis of oxybutynin, tolterodine and therapeutically equivalent salts thereof;

calcium channel blockers of nifedipine, verapamil, isradipin, nilvadipin, flunarizine, nimodipine, diltiazem, nicardipine, nisoldipin, felodipin, amlodipin, cinarizin and pendilin and pharmaceutically acceptable derivatives thereof;

beta-adrenergic antagonists of propranolol, metoprolol and pharmaceutically acceptable derivatives thereof;

angiotensin-converting enzyme inhibitors of captopril, enalapril, ramipril, fosinopril, altiopril, benazepril, libenzapril, alacepril, cilazapril, cilazaprilat, perindopril, zofedopril, lisinopril, imidapril, spirapril, rentiapril, delapril, alindapril, indalapril, quinalapril and therapeutically equivalent salts thereof;

non-steroidal anti-inflammatory agents of ketorolac, ketoprofen, benoxaprofen, caprofen, flubiprofen, fenoprofen, suprofen, fenbufen, ibuprofen, indoprofen, naproxen, miroprofen, oxaprozine, pranoprofen, pirprofen, thiaprofenic acid, fluprofen, alminoprofen, bucloxic acid, alclofenac acematacin, aspirin, indomethacin, ibufenac, isoxepac, profenac, fentiazac, clidanac, oxpinac, sulindac, tolmetin, zomepirac, zidometacin, tenclofenac, tiopinac, mefenamic acid, flufenamic acid, niflumic acid, meclofenamic acid, tolfenamic acid, diflufenisal, isoxicam, sudoxicam and therapeutically equivalent salts thereof;

therapeutic agents for respiratory disorders of theophylline, salbutamol, aminophylline, dextromethorphan, pseudoephedrine and therapeutically equivalent salts thereof;

analgesics of tramadol, acetaminophen, morphine, hydromorphone, oxycodone, propoxyphene and therapeutically equivalent salts thereof;

psychoneural drugs of fluoxetine, paroxetine, buspirone, carmabazepine, carvidopa, levodopa, methylphenidate, trazodone, valproic acid, amitriptyline, carbamazepine,

ergoloid, haloperidol, lorazepam and therapeutically equivalent salts thereof;

antibiotics of azithromycin dihydrate, cepha antibiotics, clarithromycin, doxycycline, nitrofurantonin and therapeutically equivalent salts thereof;

antihyperlipidemic agent of bezafibrate, fenofibrate, ethofibrate, lovastatin and therapeutically equivalent salts thereof;

antidiabetic agent of glyburide, glipizide, metformin and therapeutically equivalent salts thereof; and

cyclobenzaprin, favotidin, nizatidine, propafenone, clonazepam, hyoscyamine, diphenhydramine, olistat, doxazosin and therapeutically equivalent salts thereof.

14. The controlled-release oral preparation in Claim 1, wherein the drug is released in zero-order over at least 8 to 24 hr upon the administration of the preparation.

15. The controlled-release oral preparation in Claim 1, wherein by erosion of the surface of matrix, 0 to 20% of total granules is released over 0 to 4 hr, 0 to 50% is released over 0 to 8 hr, 0 to 70% is released over 0 to 16hr, and 0 to 100% is released over 0 to 24 hr.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00200

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC:A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
CAPLUS(STN), PROMT(STN), SCISEARCH(STN), INVESTEXT(STN), INSPEC(STN), COMPENDEX(STN), PASCAL(STN), CABA(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** COMBINATION OF SELECTED OPIOIDS WITH OTHER ACTIVE SUBSTANCES FOR USE IN THE THERAPY OF URINARY INCONTINENCE

(54) **Bezeichnung:** KOMBINATION AUSGEWÄHLTER OPIOIDE MIT ANDEREN WIRKSTOFFEN ZUR THERAPIE DER HARNINKONTINENZ

(57) **Abstract:** The invention relates to the use of a combination of the compounds of group A, especially opioids, with the compounds of group B for producing a drug for the treatment of urinary urgency or urinary incontinence. The invention also relates to corresponding drugs and to a method for treating urinary urgency or urinary incontinence.

(57) **Zusammenfassung:** Die Erfindung betrifft die Verwendung einer Kombination von Verbindungen der Gruppe A, insbesondere Opioiden, und Verbindungen der Gruppe B zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

WO 03/099268 A1

Patentanmeldung der Grünenthal GmbH, D-52078 Aachen
(eigenes Zeichen: G 3132)

Kombination ausgewählter Opioide mit anderen Wirkstoffen zur Therapie der Harninkontinenz

Die Erfindung betrifft die Verwendung einer Kombination von Verbindungen der Gruppe A, insbesondere Opioiden, und Verbindungen der Gruppe B, zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz sowie entsprechende Arzneimittel und Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

Harninkontinenz ist der unwillkürliche Harnabgang. Dieser tritt unkontrolliert auf, wenn der Druck innerhalb der Harnblase den Druck übersteigt, der zum Schließen des Harnleiters notwendig ist. Ursachen können zum einen ein erhöhter interner Blasendruck (z. B. durch Detrusorinstabilität) mit der Folge der Dranginkontinenz und zum anderen ein erniedrigter Sphinkterdruck (z. B. nach Geburt oder chirurgischen Eingriffen) mit der Folge der Streßinkontinenz sein. Der Detrusor ist die grob gebündelte mehrschichtige Blasenwandmuskulatur, deren Kontraktion zur Harnentleerung führt, der Sphinkter der Schließmuskel der Harnröhre. Es treten Mischformen dieser Inkontinenzarten sowie die sogenannte Überfluß-inkontinenz (z. B. bei benigner Prostatahyperplasie) oder Reflexinkontinenz (z. B. nach Rückenmarksschädigungen) auf. Näheres dazu findet sich bei Chutka, D. S. und Takahashi, P. Y., 1998, Drugs 560: 587-595.

Harndrang ist der auf Harnentleerung (Miktion) abzielende Zustand vermehrter Blasenmuskelspannung bei Annäherung an die Blasenkapazität (bzw. bei deren Überschreitung). Dabei wirkt diese Anspannung als Miktionsreiz. Unter einem vermehrten Harndrang versteht man dabei insbe-

sondere das Auftreten vorzeitigen oder gehäuften manchmal sogar schmerzhaften Harndrangs bis hin zum sog. Harnzwang. Das führt in der Folge zu einer deutlich häufigeren Miktion. Ursachen können u.a. Harnblasenentzündungen und neurogene Blasenstörungen sowie auch Blasentuberkulose sein. Es sind aber noch nicht alle Ursachen geklärt.

Vermehrter Harndrang wie auch Harninkontinenz werden als extrem unangenehm empfunden und es besteht ein deutlicher Bedarf bei von diesen Indikationen betroffenen Personen, eine möglichst langfristige Verbesserung zu erreichen.

Üblicherweise werden vermehrter Harndrang und insbesondere Harninkontinenz medikamentös mit Substanzen behandelt, die an den Reflexen des unteren Harntraktes beteiligt sind (Wein, A. J., 1998, Urology 51 (Suppl. 21): 43 – 47). Meistens sind dies Medikamente, die eine hemmende Wirkung auf den Detrusormuskel, der für den inneren Blasendruck verantwortlich ist, haben. Diese Medikamente sind z. B. Parasympatholytika wie Oxybutynin, Propiverin oder Tolterodin, trizyklische Antidepressiva wie Imipramin oder Muskelrelaxantien wie Flavoxat. Andere Medikamente, die insbesondere den Widerstand der Harnröhre oder des Blasenhalses erhöhen, zeigen Affinitäten zu α-Adrenorezeptoren wie Ephedrin, zu β-Adrenorezeptoren wie Clenbutarol oder sind Hormone wie Östradiol.

Einen genauen Einblick in die verwendeten Therapeutika und Therapiemethoden, insbesondere bezüglich der Antimuskarinika und anderer peripher wirkender Stoffe, gibt hier der Übersichtsartikel von K.E. Andersson et al. „The pharmacological treatment of urinary incontinence",. BJU International (1999), 84, 923 – 947.

Auch bestimmte Diarylmethylpiperazine und –piperidine sind für diese Indikation in der WO 93/15062 beschrieben. Ebenso wurde für Tramadol ein positiver Effekt auf die Blasenfunktion in einem Rattenmodell

rhythmischer Blasenkontraktionen nachgewiesen (Nippon-Shinyaku, WO 98/46216). Weiterhin gibt es in der Literatur Untersuchungen zur Charakterisierung der opioiden Nebenwirkung Harnretention, woraus sich einige Hinweise auf die Beeinflussung der Blasenfunktionen durch schwache Opioide wie Diphenoxylat (Fowler et al., 1987 J. Urol 138:735-738) und Meperidin (Doyle and Briscoe, 1976 Br J Urol 48:329-335), durch gemischte Opioidagonisten / -antagonisten wie Buprenorphin (Malinovsky et al., 1998 Anesth Analg 87:456-461; Drenger and Magora, 1989 Anesth Analg 69:348-353), Pentazocin (Shimizu et al. (2000) Br. J. Pharmacol. 131 (3): 610 – 616) und Nalbuphin (Malinovsky et al., 1998, a.a.O), sowie durch starke Opioide wie Morphin (Malinovsky et al., 1998 a.a.O; Kontani und Kawabata, (1988); Jpn J Pharmacol. Sep;48(1):31) und Fentanyl (Malinovsky et al., 1998 a.a.O) ergeben. Allerdings erfolgten diese Untersuchungen zumeist in analgetisch wirksamen Konzentrationen.

Bei den hier in Frage kommenden Indikationen ist zu beachten, daß es sich im allgemeinen um sehr langfristige medikamentöse Anwendungen handelt und sich die Betroffenen im Gegensatz zu vielen Situationen, in denen Analgetika eingesetzt werden, einer sehr unangenehmen, aber nicht unaushaltbaren Situation gegenüber sehen. Daher ist hier - noch mehr als bei Analgetika - darauf zu achten, Nebenwirkungen zu vermeiden, will der Betroffene nicht ein Übel gegen das andere tauschen. Auch sind bei einer dauerhaften Harninkontinenzbehandlung auch analgetische Wirkungen weitgehend unerwünscht.

Aufgabe der vorliegenden Erfindung war es daher, Stoffe oder Stoffkombinationen aufzufinden, die zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz hilfreich sind und bei den wirksamen Dosen bevorzugt gleichzeitig geringere Nebenwirkungen und/oder analgetische Wirkungen zeigen als aus dem Stand der Technik bekannt, insbesondere einen synergistischen Effekt zur Behandlung der Harninkontinenz zeigen.

Überraschenderweise wurde nun gefunden, daß eine Kombination aus Verbindungen der Gruppe A, die Opioide und andere zentralwirkende Substanzen, die mit Opioid-Rezeptoren wechselwirken und deren Effekte durch Naloxon antagonisiert werden können, oder insbesondere Substanzen, die über einen Opiat-Rezeptor, insbesondere den μ-Rezeptor, wirken, umfaßt, und Verbindungen der Gruppe B, die Muskarinantagonisten, und andere überwiegend peripher wirkende, in der Harninkontinenz bekanntermaßen wirksame Substanzen umfaßt, eine hervorragende Wirkung auf die Blasenfunktion besitzen. Weiter erwiesen sich diese Kombinationen - deutlich über das Erwartete hinaus - bereits bei sehr geringen Dosen als so wirksam, daß die kombinierten Wirkstoffe niedrig dosiert eingesetzt werden konnten. Dadurch ist zu erwarten, daß sonst bei höheren notwendigen Dosierungen auftretende Nebenwirkungen deutlich zurückgehen werden, während die therapeutische Wirkung durch diese Kombination aus peripherem, überwiegend direkt auf die Blase oder Blasenmuskulatur wirkendem, antimuskarinem Effekt und zentralem Opioid-Effekt bzw. μ-Rezeptor-Effekt voll erhalten bleibt.

Dementsprechend ist Erfindungsgegenstand die Verwendung einer Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol, oder O-desmethyl-N-mono-desmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder

Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

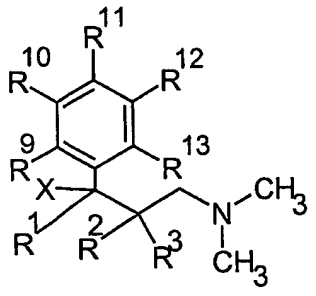
- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide

- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

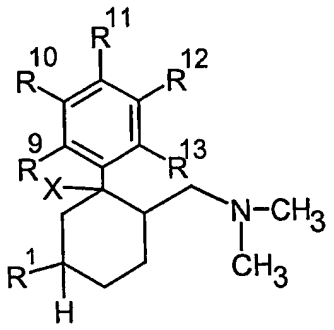
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder

ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert;
Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

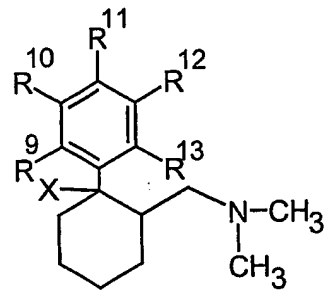
R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,
als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form

der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt

oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

den Antimuskarinika: Atropin, Oxybutinin, Propiverin, Propanthelin, Emepronium, Trospium, Tolterodin, Darifenacin und α,α-Diphenylessigsäure-4-(N-methyl-piperidyl)-ester, sowie Duloxetin, Imipramin und Desmopressin,

sowie

Venlafaxin, Fesoterodin, Solifenacin (YM905), Resiniferatoxin, Cizolirtine, Nitro-Flurbiprofen, HCT1026,

Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

zur Herstellung eines Arzneimittels zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz.

Überraschenderweise hatte sich herausgestellt, daß die Kombination der genannten Substanzen bestimmte physiologische Parameter, die bei vermehrtem Harndrang bzw. Harninkontinenz von Bedeutung sind, deutlich positiv beeinflußen. Jede einzelne dieser Veränderungen kann eine deutliche Erleichterung im symptomatischen Bild von betroffener Patienten bedeuten.

Die Verbindungen der Gruppe B wirken überwiegend peripher in der Harninkontinenz. Dabei ist Venlafaxin ein selektiver Noradrenalin Reuptake Inhibitor mit Wirksamkeit in der Stressinkontinenz (Bae J.H. et al., BJU International 2001, 88, 771, 775). Fesoterodin ist ein von Schwarz Pharma entwickelter mACh Antagonist. Solifenacin (YM905) ist ein von Yamanouchi entwickelter mACh Antagonist. Resiniferatoxin ist ein von Afferon, Mundipharma und ICOS entwickelter VR1-Agonist (allerdings insbesondere zur lokalen Anwendung). Cizolirtine ist eine im Europäischen Patent EP 289 380 B1 beschriebene Verbindung (2-[phenyl(1-methyl-1H-pyrazole-5-yl)methoxy]-N,N-dimethylethanamine, die auch als 5-[alpha -(2-

dimethylaminoethoxy)benzyl]-1-methyl-1H-pyrazole oder 5-{[N,N-dimethylaminoethoxy)phenyl]methyl}-1-methyl-1H-pyrazole) bezeichnet werden kann) mit bisher unbekanntem Wirkmechanismus, die von der Firma Esteve (ES) klinisch in der Harninkontinenz untersucht wird. Nitro-Flurbiprofen und HCT-1026 sind zwei von NicOx entwickelte auf NO + COX wirkende Stoffe. Talnetant ist ein von Glaxo Smith Kline entwickelter NK Antagonist. TAK-637 ist ein von Takeda entwickelter NK Antagonist. SL 251039 ist ein von Sanofi entwickelter a_1AR Agonist. R 450 ist ein von Roche entwickelter a_1AR Agonist. Rec 15/3079 ist ein von Recordati entwickelter $5HT_{1A}$-Antagonist. (-)-DDMS ist eine von Sepracor entwickelte Substanz, die auf NA + D wirkt. NS-8 ist eine von Nippon Shinyaku entwickelte Substanz, die auf PCA wirkt. DRP-001 ist eine von Sosei für die Dranginkontionenz entwickelte Substanz mit unbekanntem Wirkmechanismus.

Im Sinne dieser Erfindung versteht man unter Alkyl- bzw. Cykloalkyl-Resten gesättigte und ungesättigte (aber nicht aromatische), verzweigte, unverzweigte und cyclische Kohlenwasserstoffe, die unsubstituiert oder ein- oder mehrfach substituiert sein können. Dabei steht C_{1-2}-Alkyl für C1- oder C2-Alkyl, C_{1-3}-Alkyl für C1-, C2- oder C3-Alkyl, C_{1-4}-Alkyl für C1-, C2-, C3- oder C4-Alkyl, C_{1-5}-Alkyl für C1-, C2-, C3-, C4- oder C5-Alkyl, C_{1-6}-Alkyl für C1-, C2-, C3-, C4-, C5- oder C6-Alkyl, C_{1-7}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6- oder C7-Alkyl, C_{1-8}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7- oder C8-Alkyl, C_{1-10}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8,- C9- oder C10-Alkyl und C_{1-18}-Alkyl für C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8,- C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- oder C18-Alkyl. Weiter steht C_{3-4}-Cycloalkyl für C3- oder C4-Cycloalkyl, C_{3-5}-Cycloalkyl für C3-, C4- oder C5-Cycloalkyl, C_{3-6}-Cycloalkyl für C3-, C4-, C5- oder C6-Cycloalkyl, C_{3-7}-Cycloalkyl für C3-, C4-, C5-, C6- oder C7-Cycloalkyl, C_{3-8}-Cycloalkyl für C3-, C4-, C5-, C6-, C7- oder C8-Cycloalkyl, C_{4-5}-Cycloalkyl für C4- oder C5-Cycloalkyl, C_{4-6}-Cycloalkyl für C4-, C5- oder C6-Cycloalkyl, C_{4-7}-Cycloalkyl für C4-, C5-, C6- oder C7-Cycloalkyl, C_{5-6}-Cycloalkyl für C5- oder C6-

Cycloalkyl und C_{5-7}-Cycloalkyl für C5-, C6- oder C7-Cycloalkyl. In Bezug auf Cycloalkyl umfaßt der Begriff auch gesättigte Cycloalkyle, in denen ein oder 2 Kohlenstoffatome durch ein Heteroatom, S, N oder O ersetzt sind. Unter den Begriff Cycloalkyl fallen aber insbesondere auch ein- oder mehrfach, vorzugsweise einfach, ungesättigte Cycloalkyle ohne Heteroatom im Ring, solange das Cycloalkyl kein aromatisches System darstellt. Vorzugsweise sind die Alkyl- bzw. Cykloalkyl-Reste Methyl, Ethyl, Vinyl (Ethenyl), Propyl, Allyl (2-Propenyl), 1-Propinyl, Methylethyl, Butyl, 1-Methylpropyl, 2-Methylpropyl, 1,1-Dimethylethyl, Pentyl, 1,1-Dimethylpropyl, 1,2-Dimethylpropyl, 2,2-Dimethylpropyl, Hexyl, 1-Methylpentyl, Cyclopropyl, 2-Methylcyclopropyl, Cyclopropylmethyl, Cyclobutyl, Cyclopentyl, Cyclopentylmethyl, Cyclohexyl, Cycloheptyl, Cyclooctyl, aber auch Adamantyl, CHF_2, CF_3 oder CH_2OH sowie Pyrazolinon, Oxopyrazolinon, [1,4]Dioxan oder Dioxolan.

Dabei versteht man im Zusammenhang mit Alkyl und Cycloalkyl – solange dies nicht ausdrücklich anders definiert ist - unter dem Begriff substituiert im Sinne dieser Erfindung die Substitution mindestens eines (gegebenenfalls auch mehrerer) Wasserstoffreste(s) durch F, Cl, Br, I, NH_2, SH oder OH, wobei unter „mehrfach substituiert" bzw. „substituiert" bei mehrfacher Substitution zu verstehen ist, daß die Substitution sowohl an verschiedenen als auch an gleichen Atomen mehrfach mit den gleichen oder verschiedenen Substituenten erfolgt, beispielsweise dreifach am gleichen C-Atom wie im Falle von CF_3 oder an verschiedenen Stellen wie im Falle von -CH(OH)-CH=CH-$CHCl_2$. Besonders bevorzugte Substituenten sind hier F, Cl und OH. In Bezug auf Cycloalkyl kann der Wasserstoffrest auch durch OC_{1-3}-Alkyl oder C_{1-3}-Alkyl (jeweils ein- oder mehrfach substituiert oder unsubstituiert), insbesondere Methyl, Ethyl, n-Propyl, i-Propyl, CF_3, Methoxy oder Ethoxy, ersetzt sein.

Unter dem Begriff $(CH_2)_{3-6}$ ist -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-CH_2- und CH_2-CH_2-CH_2-CH_2-CH_2-CH_2- zu verstehen, unter

$(CH_2)_{1-4}$ ist $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ und $-CH_2-CH_2-CH_2-CH_2-$ zu verstehen, unter $(CH_2)_{4-5}$ ist $-CH_2-CH_2-CH_2-CH_2-$ und $-CH_2-CH_2-CH_2-CH_2-CH_2-$ zu verstehen, etc.

Unter einem Aryl-Rest werden Ringsysteme mit mindestens einem armomatischen Ring aber ohne Heteroatome in auch nur einem der Ringe verstanden. Beispiele sind Phenyl-, Naphthyl-, Fluoranthenyl-, Fluorenyl-, Tetralinyl- oder Indanyl, insbesondere 9H-Fluorenyl- oder Anthracenyl-Reste, die unsubstituiert oder einfach oder mehrfach substituiert sein können.

Unter einem Heteroaryl-Rest werden heterocyclische Ringsysteme mit mindestens einem ungesättigten Ring verstanden, die ein oder mehrere Heteroatome aus der Gruppe Stickstoff, Sauerstoff und/oder Schwefel enthalten und auch einfach oder mehrfach substituiert sein können. Beispielhaft seien aus der Gruppe der Heteroaryle Furan, Benzofuran, Thiophen, Benzothiophen, Pyrrol, Pyridin, Pyrimidin, Pyrazin, Chinolin, Isochinolin, Phthalazin, Benzo-1,2,5 thiadiazol, Benzothiazol, Indol, Benzotriazol, Benzodioxolan, Benzodioxan, Carbazol, Indol und Chinazolin aufgeführt.

Dabei versteht man im Zusammenhang mit Aryl und Heteroaryl unter substituiert die Substitution des Aryls oder Heteroaryls mit R^{23}, OR^{23} einem Halogen, vorzugsweise F und/oder Cl, einem CF_3, einem CN, einem NO_2, einem $NR^{24}R^{25}$, einem C_{1-6}-Alkyl (gesättigt), einem C_{1-6}-Alkoxy, einem C_{3-8}-Cycloalkoxy, einem C_{3-8}-Cycloalkyl oder einem C_{2-6}-Alkylen.

Dabei steht der Rest R^{23} für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl- oder Heteroaryl- oder für einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest, wobei diese Aryl

und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen,

die Reste R^{24} und R^{25}, gleich oder verschieden, für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl-, einen Heteroaryl- oder einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest bedeuten, wobei diese Aryl und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen,

oder die Reste R^{24} und R^{25} bedeuten zusammen $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{26}CH_2CH_2$ oder $(CH_2)_{3-6}$, und

der Rest R^{26} für H, einen C_{1-10}-Alkyl-, vorzugsweise einen C_{1-6}-Alkyl-, einen Aryl-, oder Heteroaryl- Rest oder für einen über eine C_{1-3}-Alkylen-Gruppe gebundenen Aryl- oder Heteroaryl-Rest, wobei diese Aryl und Heteroarylreste nicht selbst mit Aryl- oder Heteroaryl-Resten substituiert sein dürfen.

Unter dem Begriff Salz ist jegliche Form des erfindungsgemäßen Wirkstoffes zu verstehen, in dem dieser eine ionische Form annimmt bzw. geladen ist und mit einem Gegenion (einem Kation oder Anion) gekoppelt ist bzw. sich in Lösung befindet. Darunter sind auch Komplexe des Wirkstoffes mit anderen Molekülen und Ionen zu verstehen, insbesondere Komplexe, die über ionische Wechselwirkungen komplexiert sind.

Unter dem Begriff des physiologisch verträglichen Salzes mit Kationen oder Basen versteht man im Sinne dieser Erfindung Salze mindestens einer der erfindungsgemäßen Verbindungen - meist einer (deprotonierten) Säure - als Anion mit mindestens einem, vorzugsweise anorganischen, Kation, die physiologisch – insbesondere bei Anwendung im Menschen und/oder

Säugetier – verträglich sind. Besonders bevorzugt sind die Salze der Alkali- und Erdalkalimetalle aber auch mit NH_4^+, insbesondere aber (Mono-) oder (Di-) Natrium-, (Mono-) oder (Di-) Kalium-, Magnesium- oder Calzium-Salze.

Unter dem Begriff des physiologisch verträglichen Salzes mit Anionen oder Säuren versteht man im Sinne dieser Erfindung Salze mindestens einer der erfindungsgemäßen Verbindungen – meist, beispielsweise am Stickstoff, protoniert - als Kation mit mindestens einem Anion, die physiologisch – insbesondere bei Anwendung im Menschen und/oder Säugetier – veträglich sind. Insbesondere versteht man darunter im Sinne dieser Erfindung das mit einer physiologisch verträglichen Säure gebildete Salz, nämlich Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren, die physiologisch - insbesondere bei Anwendung im Menschen und/oder Säugetier - verträglich sind. Beispiele für physiologisch verträgliche Salze bestimmter Säuren sind Salze der: Salzsäure, Bromwasserstoffsäure, Schwefelsäure, Methansulfonsäure, Ameisensäure, Essigsäure, Oxalsäure, Bernsteinsäure, Apfelsäure, Weinsäure, Mandelsäure, Fumarsäure, Milchsäure, Zitronensäure, Glutaminsäure, 1,1-Dioxo-1,2-dihydro1b6-benzo[d]isothiazol-3-on (Saccharinsäure), Monomethylsebacinsäure, 5-Oxo-prolin, Hexan-1-sulfonsäure, Nicotinsäure, 2-, 3- oder 4-Aminobenzoesäure, 2,4,6-Trimethyl-benzoesäure, a-Liponsäure, Acetylglycin, Acetylsalicylsäure, Hippursäure und/oder Asparaginsäure. Besonders bevorzugt ist das Hydrochlorid-Salz.

Geeignete Salze im Sinne dieser Erfindung und in jeder beschriebenen Verwendung und jedem der beschriebenen Arzneimittel sind Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren und/oder einem Zuckeraustauschstoff wie Saccharin, Cyclamat oder Acesulfam. Besonders bevorzugt ist jedoch das Hydrochlorid.

Verbindungen der **Gruppe c)** und deren Herstellung sind aus der DE 44 26 245 A1 bzw. der US 6,248,737 bekannt. Verbindungen der **Gruppe d)** und **e)** und deren Herstellung sind aus der DE 195 25 137 A1 bzw. US 5,733,936 bzw. US RE37355E bekannt.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe a**) ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe b**) ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin
- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

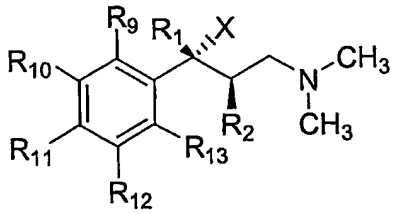
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

Dabei ist es für Verbindungen der **Gruppe c)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-

phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe d)** ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

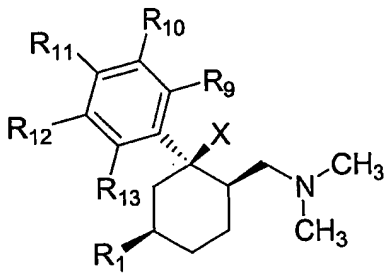
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe d)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden,

und/oder

daß die Verbindungen der **Formel II** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

In einer bevorzugten Ausführungsform gilt für die erfindungsgemäße Verwendung, daß die **Verbindung A** in **Gruppe e)** ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

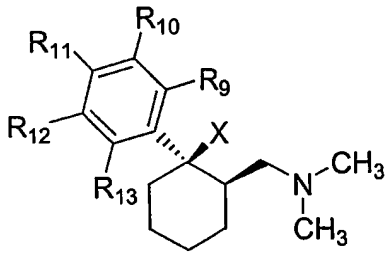
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe e)** besonders bevorzugt, wenn gilt, daß Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer verwendet werden

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer verwendet werden.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt aus folgender Gruppe verwendet wird:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

Für eine besonders bevorzugte Verwendung gilt, daß die **Verbindung B** ausgewählt ist aus:

Darifenacin, Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Oxybutinin oder Tolterodin.

Für eine andere besonders bevorzugte Verwendung gilt, daß die **Verbindung B** ausgewählt ist aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, oder Resiniferatoxin.

Auch wenn die erfindungsgemässen Verwendungen lediglich geringe Nebenwirkungen zeigen, kann es beispielsweise zur Vermeidung von bestimmten Formen der Abhängigkeit auch von Vorteil sein, neben der Kombination der **Verbindungen A** und **B** auch Morphinantagonisten, insbesondere Naloxon, Naltrexon und/oder Levallorphan, zu verwenden.

Ein weiterer Gegenstand der Erfindung ist eine Wirkstoffkombination aus wenigstens einer der **Verbindungen A** und wenigstens einer der **Verbindungen B**, mit **Verbindung A** ausgewählt aus:

Gruppe a) enthaltend:

Tramadol, O-Demethyltramadol oder O-desmethyl-N-monodesmethyl-tramadol als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe b) enthaltend:

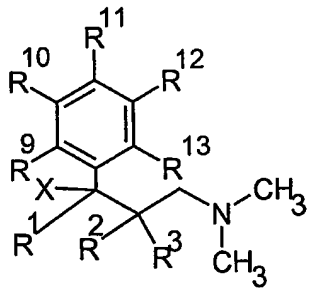
- Codein
- Dextropropxyphen

- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Tramadol
- Viminol
- Butorphanol
- Dextromoramid
- Dezocin
- Diacetylmorphin (Heroin)
- Hydrocodon
- Hydromorphon
- Ketobemidon
- Levomethadon
- Levomethadyl-Acetate (l-α-Acetylmethadol (LAAM))
- Levorphanol
- Morphin
- Nalorphin
- Oxycodon
- Pentazocin
- Piritramide
- Alfentanil
- Buprenorphin
- Etorphin
- Fentanyl
- Remifentanil
- Sufentanil

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe c) enthaltend:

1-Phenyl-3-dimethylamino-propanverbindungen gemäß allgemeiner **Formel I**



I

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^2 und R^3 jeweils unabhängig voneinander ausgewählt sind aus H oder C_{1-4}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^2 und R^3 zusammen einen gesättigten C_{4-7}-Cycloalkylrest bilden, unsubstituiert oder ein- oder mehrfach substituiert,

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die

Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

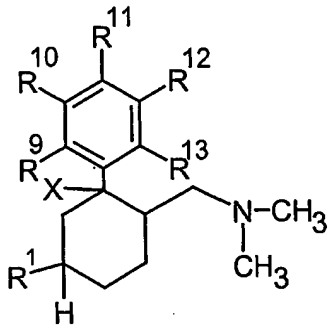
oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

Gruppe d) enthaltend:

substituierte 6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel II**



II

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert,

R^1 ausgewählt ist aus C_{1-4}-Alkyl, Benzyl, CF_3, OH, OCH_2-C_6H_5, O-C_{1-4}-Alkyl, Cl oder F und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert;

$PO(O\text{-}C_{1\text{-}4}\text{-Alkyl})_2$, $CO(OC_{1\text{-}5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1\text{-}3}\text{-Alkyl})$, $CO(C_{1\text{-}5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1\text{-}3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} $C_{1\text{-}4}$-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; $C_{1\text{-}6}$-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

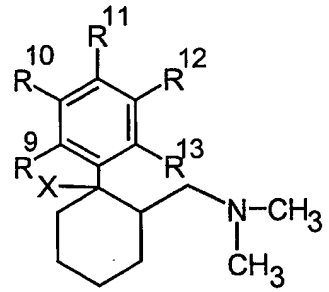
R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und/oder

Gruppe e) enthaltend:

6-Dimethylaminomethyl-1-phenyl-cyclohexanverbindungen gemäß allgemeiner **Formel III**



III

, worin

X ausgewählt ist aus OH, F, Cl, H oder $OC(O)R^7$ mit R^7 ausgewählt aus C_{1-3}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, und

R^9 bis R^{13} jeweils unabhängig voneinander ausgewählt sind aus H, F, Cl, Br, I, CH_2F, CHF_2, CF_3, OH, SH, OR^{14}, OCF_3, SR^{14}, $NR^{17}R^{18}$, $SOCH_3$, $SOCF_3$; SO_2CH_3, SO_2CF_3, CN, $COOR^{14}$, NO_2, $CONR^{17}R^{18}$; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, unsubstituiert oder ein- oder mehrfach substituiert;

mit R^{14} ausgewählt aus C_{1-6}-Alkyl; Pyridyl, Thienyl, Thiazolyl, Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert; $PO(O\text{-}C_{1-4}\text{-Alkyl})_2$, $CO(OC_{1-5}\text{-Alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-Alkyl})$, $CO(C_{1-5}\text{-Alkyl})$, $CO\text{-}CHR^{17}\text{-}NHR^{18}$, $CO\text{-}C_6H_4\text{-}R^{15}$, mit R^{15} ortho-$OCOC_{1-3}$-Alkyl oder meta- oder para-$CH_2N(R^{16})_2$ mit R^{16} C_{1-4}-Alkyl oder 4-Morpholino, wobei in den Resten R^{14}, R^{15} und R^{16} die Alkylgruppen verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert sein können;

mit R^{17} und R18 jeweils unabhängig voneinander ausgewählt aus H; C_{1-6}-Alkyl, verzweigt oder unverzweigt, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert; Phenyl, Benzyl oder Phenethyl, jeweils unsubstituiert oder ein- oder mehrfach substituiert,

oder

R^9 und R^{10} oder R^{10} und R^{11} zusammen einen OCH_2O-, OCH_2CH_2O-, OCH=CH-, CH=CHO-, CH=C(CH3)O-, OC(CH3)=CH-, $(CH_2)_4$- oder OCH=CHO-Ring bilden,

mit der Maßgabe, daß, wenn R^9, R^{11} und R^{13} H entsprechen, und einer von R^{10} oder R^{12} H und der andere OCH_3 entspricht, X nicht OH sein darf,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch

verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren; in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers;

und mit wenigstens einer der **Verbindungen B**, ausgewählt aus:

den Antimuskarinika: Atropin, Oxybutinin, Propiverin, Propanthelin, Emepronium, Trospium, Tolterodin, Darifenacin und α,α-Diphenylessigsäure-4-(N-methyl-piperidyl)-ester, sowie Duloxetin, Imipramin und Desmopressin,

sowie

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine, Resiniferatoxin, Nitro-Flurbiprofen, HCT1026, Talnetant, TAK-637, SL 251039, R 450, Rec 15/3079, (-)-DDMS, NS-8 und/oder DRP-001,

als freie Base oder Säure und/oder in Form physiologisch verträglicher Salze, insbesondere in Form ihrer physiologisch verträglichen sauren und basischen Salze bzw. Salze mit Kationen bzw. Basen oder mit Anionen bzw. Säuren, gegebenenfalls in Form der Enantiomere, Diastereomere, insbesondere Mischungen ihrer Enantiomere oder Diastereomere oder eines einzelnen Enantiomers oder Diastereomers.

Geeignete Salze im Sinne dieser Erfindung und in jedem der beschriebenen Arzneimittel sind Salze des jeweiligen Wirkstoffes mit anorganischen bzw. organischen Säuren und/oder einem Zuckeraustauschstoff wie Saccharin, Cyclamat oder Acesulfam. Besonders bevorzugt ist jedoch das Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe a**) ausgewählt ist aus:

Tramadol, (+)-Tramadol, (+)-O-Demethyltramadol oder (+)-O-desmethyl-N-mono-desmethyl-tramadol,
vorzugsweise Tramadol oder (+)-Tramadol,
insbesondere (+)-Tramadol.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe b**) ausgewählt ist aus:

- Codein
- Dextropropxyphen
- Dihydrocodein
- Diphenoxylat
- Ethylmorphin
- Meptazinol
- Nalbuphin
- Pethidin (Meperidine)
- Tilidin
- Viminol
- Butorphanol
- Dezocin
- Nalorphin
- Pentazocin

- Buprenorphin

, vorzugsweise

- Codein
- Dextropropxyphen
- Dihydrocodein
- Meptazinol
- Nalbuphin
- Tilidin
- Buprenorphin

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe c)** ausgewählt ist aus Verbindungen gemäß **Formel I** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F, $OC(O)CH_3$ oder H,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise CH_3, C_2H_5, C_4H_9 oder t-Butyl, insbesondere CH_3 oder C_2H_5,

und/oder

R^2 und R^3 unabhängig voneinander ausgewählt sind aus

H, C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; vorzugsweise H, CH_3, C_2H_5, i-Propyl oder t-Butyl, insbesondere H oder CH_3, vorzugsweise R^3 = H,

oder

R^2 und R^3 zusammen einen C_{5-6}-Cycloalkylrest bilden, gesättigt oder ungesättigt, unsubstituiert oder ein- oder mehrfach substituiert, vorzugsweise gesättigt und unsubstituiert, insbesondere Cyclohexyl.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OCH_3 oder SCH_3

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

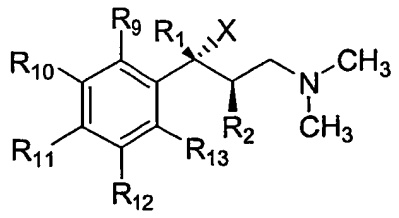
oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7.

Dabei ist es für Verbindungen der **Gruppe c)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel I** mit R^3 = H in Form der Diastereomeren mit der relativen Konfiguration Ia



Ia

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol,
- (3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol,
- (2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol,
- (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol,
- (+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester,
- (1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-

phenyl)-propan-1-ol,
- (2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol,
- (+)-(2R,3R)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol,
- (2RS,3RS)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol und
- (+)-(2R,3R)-4-Dimethylamino-2-(3-methoxy-phenyl)-3-methyl-butan-2-ol,

vorzugsweise als Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe d**) ausgewählt ist aus Verbindungen gemäß **Formel II** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere OH,

und/oder

R^1 ausgewählt ist aus

C_{1-4}-Alkyl, CF_3, OH, O-C_{1-4}-Alkyl, Cl oder F, vorzugsweise OH, CF_3 oder CH_3,

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden,

insbesondere

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

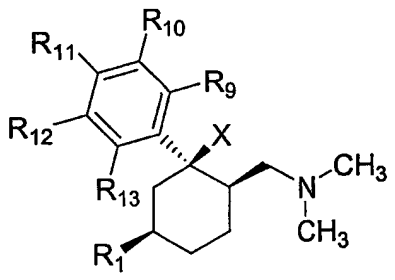
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe d)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel II** in Form der Diastereomeren mit der relativen Konfiguration IIa



IIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer,

und/oder

daß die Verbindungen der **Formel I** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol,
- (1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol,
- (+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol oder
- (1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

Für die Wirkstoffkombination ist es besonders bevorzugt, wenn gilt, daß die **Verbindung A** in **Gruppe e**) ausgewählt ist aus Verbindungen gemäß **Formel III** für die gilt, daß:

X ausgewählt ist aus

OH, F, Cl, $OC(O)CH_3$ oder H, vorzugsweise OH, F oder H, insbesondere F oder H.

und/oder

R^9 bis R^{13}, wobei 3 oder 4 der Reste R^9 bis R^{13} H entsprechen müssen, unabhängig voneinander ausgewählt sind aus

H, Cl, F, OH, CF_2H, CF_3 oder C_{1-4}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt; OR^{14} oder SR^{14}, mit R^{14} ausgewählt aus C_{1-3}-Alkyl, gesättigt und unsubstituiert, verzweigt oder unverzweigt;

vorzugsweise H, Cl, F, OH, CF_2H, CF_3, OCH_3 oder SCH_3

oder R^{12} und R^{11} einen 3,4-OCH=CH-Ring bilden

insbesondere dadurch gekennzeichnet, daß,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH, CF_2H, OR^{14} oder SCH_3, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3,

oder,

wenn R^9 und R^{13} H entsprechen und R^{11} OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht, einer von R^{10} oder R^{12} auch H entspricht, während der andere OH, OCH_3, Cl oder F, vorzugsweise Cl, entspricht,

oder,

wenn R^9, R^{10}, R^{12} und R^{13} H entsprechen, R^{11} ausgewählt ist aus CF_3, CF_2H, Cl oder F, vorzugsweise F,

oder,

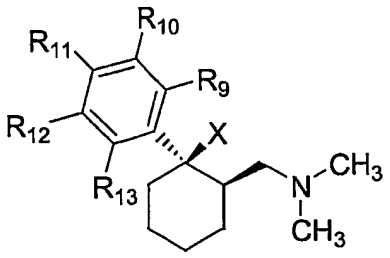
wenn R^{10}, R^{11} und R^{12} H entsprechen, einer von R^9 oder R^{13} auch H entspricht, während der andere ausgewählt ist aus OH, OC_2H_5 oder OC_3H_7,

ganz insbesondere bevorzugt,

wenn R^9, R^{11} und R^{13} H entsprechen, einer von R^{10} oder R^{12} auch H entspricht, während der andere ausgewählt ist aus:

Cl, F, OH, SH, CF_2H, CF_3, OR^{14} oder SR^{14}, vorzugsweise OH oder OR^{14}, insbesondere OH oder OC_{1-3}-Alkyl, vorzugsweise OH oder OCH_3.

Dabei ist es für Verbindungen der **Gruppe e)** besonders bevorzugt, wenn gilt, daß die Verbindungen der **Formel III** in Form ihrer Diastereomeren mit der relativen Konfiguration IIIa



IIIa

vorliegen, insbesondere in Mischungen mit höherem Anteil dieses Diastereomeren im Vergleich zum anderen Diastereomeren oder als reines Diastereomer

und/oder

, daß die Verbindungen der **Formel III** in Form des (+)-Enantiomeren, insbesondere in Mischungen mit höherem Anteil des (+)-Enantiomeren im Vergleich zum (-)-Enantiomeren einer racemischen Verbindung oder als reines (+)-Enantiomer vorliegen.

Dabei ist es besonders bevorzugt, wenn **Verbindung A** ausgewählt ist aus folgender Gruppe:

- (+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol,
- (+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol oder
- (-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol,

vorzugsweise als Hydrochlorid.

In einer generell besonders bevorzugten Form der erfindungsgemäßen Wirkstoffkombination ist die **Verbindung B** ausgewählt aus:

Darifenacin, Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Duloxetin, Oxybutinin oder Tolterodin,

vorzugsweise ausgewählt ist aus

Oxybutinin oder Tolterodin.

Für eine besonders bevorzugte Form der erfindungsgemäßen Wirkstoffkombination gilt, daß die **Verbindung B** ausgewählt ist aus:

Venlafaxin, Fesoterodin, Solifenacin (YM905), Cizolirtine oder Resiniferatoxin.

Ein weiterer Gegenstand der Erfindung ist ein Arzneimittel, vorzugsweise zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, enthaltend eine erfindungsgemäße Wirkstoffkombination sowie gegebenenfalls geeignete Zusatz- und/oder Hilfsstoffe.

Geeignete Zusatz- und/oder Hilfsstoffe im Sinne dieser Erfindung sind alle dem Fachmann aus dem Stand der Technik bekannten Stoffe zur Erreichung galenischer Formulierungen. Die Auswahl dieser Hilfsstoffe sowie die einzusetzenden Mengen derselben hängen davon ab, ob das Arzneimittel oral, intravenös, intraperitoneal, intradermal, intramuskulär, intranasal, buccal oder lokal appliziert werden soll. Für die orale Applikation eignen sich Zubereitungen in Form von Tabletten, Kautabletten, Dragees, Kapseln, Granulaten, Tropfen, Säften oder Sirupen, für die parenterale, topische und inhalative Applikation Lösungen, Suspensionen, leicht rekonstituierbare Trockenzubereitungen sowie Sprays. Eine weitere Möglichkeit sind Suppositorien für die Anwendung im Rektum. Die Anwendung in einem Depot in gelöster Form, einer Trägerfolie oder einem Pflaster, gegebenenfalls unter Zusatz von die Hautpenetration fördernden Mitteln, sind Beispiele für geeignete perkutane Applikationsformen. Beispiele für Hilfs- und Zusatzmitteln für die oralen Applikationsformen sind Sprengmittel, Gleitmittel, Binder, Füllmittel, Formtrennmittel, gegebenenfalls Lösungsmittel, Geschmacksstoffe, Zucker, insbesondere Trägermittel, Verdünnungsmittel, Farbstoffe, Antioxidantien etc. Für Suppositorien können u.a. Wachse bzw. Fettsäureester und für parenterale Applikationsmittel Trägerstoffe, Konservierungsmittel, Suspensionshilfsmittel etc. verwendet

werden. Die an Patienten zu verabreichenden Wirkstoffmengen variieren in Abhängigkeit vom Gewicht des Patienten, von der Applikationsart und dem Schweregrad der Erkrankung. Aus oral, rektal oder perkutan anwendbaren Zubereitungsformen können die erfindungsgemäßen Verbindungen verzögert freigesetzt werden. Bei der erfindungsgemäßen Indikation sind entsprechende Retard-Formulierungen, insbesondere in Form eines „Once-daily"-Präparats, das nur einmal am Tag eingenommen werden muß, besonders bevorzugt.

Weiter bevorzugt sind Arzneimittel, die wenigstens 0,05 bis 90,0 % des Wirkstoffes enthalten, insbesondere niedrige wirksame Dosierungen, um Neben- oder analgetische Wirkungen zu vermeiden. Üblicherweise werden 0,1 bis 5000 mg/kg, insbesondere 1 bis 500 mg/kg, vorzugsweise 2 bis 250 mg/kg Körpergewicht wenigstens einer Verbindung der Formel I appliziert. Ebenso bevorzugt und üblich ist aber auch die Applikation von 0,01 – 5 mg/kg, vorzugsweise 0,03 bis 2 mg/kg, insbesondere 0,05 bis 1 mg/kg Körpergewicht.

Hilfsstoffe können beispielsweise sein: Wasser, Ethanol, 2-Propanol, Glycerin, Ethylenglycol, Propylenglycol, Polyethylenglycol, Polypropylenglycol, Glucose, Fructose, Lactose, Saccharose, Dextrose, Melasse, Stärke, modifizierte Stärke, Gelatine, Sorbitol, Inositol, Mannitol, mikrokristalline Cellulose, Methylcellulose, Carboxymethylcellulose, Celluloseacetat, Schellack, Cetylalkohol, Polyvinylpyrrolidon, Paraffine, Wachse, natürliche und synthetische Gummis, Akaziengummi, Alginate, Dextran, gesättigte und ungesättigte Fettsäuren, Stearinsäure, Magnesiumstearat, Zinkstearat, Glycerylstearat, Natriumlaurylsulfat, genießbare Öle, Sesamöl, Kokusnußöl, Erdnußöl, Sojabohnenöl, Lecithin, Natriumlactat, Polyoxyethylen- und -propylen-fettsäureester, Sorbitanfettsäureester, Sorbinsäure, Benzoesäure, Citronensäure, Ascorbinsäure, Tanninsäure, Natriumchlorid, Kaliumchlorid, Magnesiumchlorid, Calciumchlorid, Magnesiumoxid, Zinkoxid,

Siliciumdioxid, Titanoxid, Titandioxid, Magnesiumsulfat, Zinksulfat, Calciumsulfat, Pottasche, Calciumphosphat, Dicalciumphosphat, Kaliumbromid, Kaliumiodid, Talkum, Kaolin, Pectin, Crospovidon, Agar und Bentonit.

Die Herstellung der erfindungsgemäßen Arzneimittel und pharmazeutischen Zusammensetzungen erfolgt mit Hilfe von im Stand der Technik der pharmazeutischen Formulierung wohlbekannten Mitteln, Vorrichtungen, Methoden und Verfahren, wie sie beispielsweise in "Remington`s Pharmaceutical Sciences", Hrsg. A.R. Gennaro, 17. Ed., Mack Publishing Company, Easton, Pa. (1985), insbesondere in Teil 8, Kapitel 76 bis 93, beschrieben sind.

So kann z.B. für eine feste Formulierung, wie eine Tablette, der Wirkstoff des Arzneimittels mit einem pharmazeutischen Träger, z.B. herkömmlichen Tabletteninhaltsstoffen, wie Maisstärke, Lactose, Saccharose, Sorbitol, Talkum, Magnesiumstearat, Dicalciumphosphat oder pharmazeutisch akzeptable Gummis, und pharmazeutischen Verdünnungsmitteln, wie z.B. Wasser, granuliert werden, um eine feste Zusammensetzungzu bilden, die Wirkstoff in homogener Verteilung enthält. Unter einer homogenen Verteilung wird hier verstanden, daß der Wirkstoff gleichmäßig über die gesamte Zusammensetzung verteilt ist, so daß diese ohne weiteres in gleich wirksame Einheitsdosis-Formen, wie Tabletten, Pillen oder Kapseln, unterteilt werden kann. Die feste Zusammensetzungwird anschließend in Einheitsdosis-Formen unterteilt. Die Tabletten oder Pillen des erfindungsgemäßen Arzneimittels bzw. der erfindungsgemäßen Zusammensetzungen können auch überzogen oder auf andere Weise kompoundiert werden, um eine Dosisform mit verzögerter Freisetzung bereitzustellen. Geeignete Beschichtungsmittel sind u.a. polymere Säuren und Mischungen von polymeren Säuren mit Materialien wie z.B. Schellack, Cetylalkohol und/oder Celluloseacetat.

Auch wenn die erfindungsgemässen Arzneimittel lediglich geringe Nebenwirkungen zeigen, kann es beispielsweise zur Vermeidung von bestimmten Formen der Abhängigkeit von Vorteil sein, neben der Kombination der **Verbindungen A** und **B** auch Morphinantagonisten, insbesondere Naloxon, Naltrexon und/oder Levallorphan, zu verwenden.

Weiter betrifft die Erfindung auch ein Verfahren zur Behandlung von vermehrtem Harndrang bzw. Harninkontinenz, bei dem die Wirkstoffkombination aus **Verbindung A** und **Verbindung B** verwendet wird.

Die folgenden Beispiele sollen die Erfindung erläutern, ohne daß der Gegenstand der Erfindung darauf beschränkt wäre.

Beispiele

Beispiel 1: Liste der getesteten Substanzen:

Es folgt eine Liste der auf ihre Wirksamkeit getesteten Verbindungen:

Name	Verbdg. Nr.
(2RS,3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	1
(+)-(2R,3R)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	2
(2RS,3RS)-3-(3,4-Dichlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	3
(2RS,3RS)-3-(3-Difluoromethyl-phenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	4
(2RS,3RS)-1-Dimethylamino-2-methyl-3-(3-methylsulfanyl-phenyl)-pentan-3-ol, Hydrochlorid	5
(3RS)-1-Dimethylamino-3-(3-methoxy-phenyl)-4,4-dimethyl-pentan-3-ol, Hydrochlorid	6
(2RS,3RS)-3-(3-Dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenol, Hydrochlorid	7

(1RS,2RS)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	8
(+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	9
(+)-(1R,2R)-3-(3-Dimethylamino-1-hydroxy-1,2-dimethyl-propyl)-phenol, Hydrochlorid	10
(-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phe-nol, Hydrochlorid	11
(+)-(1R,2R)-Essigsäure-3-dimethylamino-1-ethyl-1-(3-methoxy-phenyl)-2-methyl-propylester, Hydrochlorid	12
(1RS)-1-(1-Dimethylaminomethyl-cyclohexyl)-1-(3-methoxy-phenyl)-propan-1-ol, Hydrochlorid	13
(2RS, 3RS)-3-(4-Chlorophenyl)-1-dimethylamino-2-methyl-pentan-3-ol, Hydrochlorid	14
(+)-(1R,2R)-3-(2-Dimethylaminomethyl-1-fluoro-cyclohexyl)-phenol, Hydrochlorid	18
(+)-(1S,2S)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid	19
(-)-(1R,2R)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, Hydrochlorid	20
rac-Tramadol	23
(-)-(2S,3S)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, Hydrochlorid	21
(1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	24
(+)-(1R,3R,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	25
(1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-hydroxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	26
(1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, Hydrochlorid,	27
(+)-(1R,2R,5S)-3-(2-Dimethylaminomethyl-1-hydroxy-5-methyl-cyclohexyl)-phenol, Hydrochlorid,	28
(1RS,2RS,5RS)-3-(2-Dimethylaminomethyl-1-hydroxy-5-trifluoromethyl-cyclohexyl)-phenol, Hydrochlorid.	29

Beispiel 2: Testsystem Cystometrie an der wachen naiven Ratte

Es wurden cystometrische Untersuchungen an naiven, weiblichen Sprague-Dawley-Ratten nach der Methode von Ishizuka et. al. ((1997), Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 787 – 793) durchgeführt. Drei Tage nach Implantation von Blasen- und venösen Kathetern wurden die Tiere im wachen Zustand, frei beweglich untersucht. Der Blasenkatheter wurde an einem Druckaufnehmer und eine Injektionspumpe ange-

schlossen. Die Tiere wurden in Stoffwechselkäfige gesetzt, die die Messung des Harnvolumens ermöglichten. Physiologische Kochsalzlösung wurde in die entleerte Blase infundiert (10 ml/Std.) und Blasendruck und Miktionsvolumen kontinuierlich aufgezeichnet. Nach einer Stabilisierungsphase wurde eine 20minütige Phase aufgezeichnet, die durch normale, reproduzierbare Miktionszyklen gekennzeichnet war. Es wurden unter anderem die folgenden Parameter bestimmt:

- Schwellendruck (threshold pressure TP, Blasendruck unmittelbar vor Miktion),
- Blasenkapazität (bladder capacity BC, Restvolumen nach vorhergehender Miktion plus Volumen der infudierten Lösung während der Füllungsphase),
- Interkontraktionsintervall (inter-contraction interval (ICI), das Zeitintervall zwischen den Miktionen).

Eine Erhöhung des Schwellendrucks (TP) zeigt eine wichtige therapeutische Wirkung bei einer der erfindungsgemässen Indikationen an. Auch das Interkontraktionsintervall (ICI) ist ein wichtiger Parameter zur Messung der physiologischen Wirksamkeit eines Stoffes in der Behandlung der Harninkontinenz, ebenso wie die Blasenkapazität (BC). Dabei ist es für eine Wirksamkeit aufgrund der sehr heterogenen Ursachen für die Symptomatik dieser Erkrankungsbilder nicht nötig, alle drei Parameter positiv zu beeinflussen. Es genügt daher völlig, wenn nur in einem dieser Parameter eine posive Wirkung festzustellen ist, um in der Harninkontinenz oder vermehrtem Harndrang einsetzbar zu sein.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert, wurden die Testsubstanzen **1** (1,0 mg/kg), **2** (0,1; 0,3 und 0,5 mg/kg), **21** (0,5 mg/kg), **7** (0,3 mg/kg), **8** (1,0 mg/kg), **9** (0,5 mg/kg) und **11** (0.5 mg/kg); im Vehikel = 0.9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im

Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 1).

Verbindung: (Konzentration)	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
1 1,0 mg/kg iv (n=9)	+94 % **	+31 % ***	+42 %
2 0,1 mg/kg iv (n=5)	+28,5 % **	+7,8 %	+15,6 %
0,3 mg/kg iv (n=8)	+122 %**	+33 %*	+28 %*
0,5 mg/kg iv (n=9)	+77,5 %**	+20,6 %*	+28,6 %**
21 0,5 mg/kg iv (n=8)	-1,1 %	+3 %	+10 %
7 0,3 mg/kg iv (n=7)	+95 %**	+32 %*	+28 %*
8 1,0 mg/kg iv (n=8)	+60 %**	+7 %	+14,4 %
9 0,5 mg/kg iv (n=7)	+56 %**	+50 %**	+21 %*
11 0,5 mg/kg iv (n=8)	+9 %	+11 %	+22,6

Tabelle 1: Beeinflussung der cystometrischen Parameter durch die Testsubstanzen (Veränderung zum Vorwert [%]); n entspricht der Anzahl der Versuchstiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Unter anderem zeigt sich, daß von den Enantiomeren der racemischen Verbindung 1 nur das (+)- Enantiomere (Verbindung 2) effektiv wirksam ist (und damit eine besonders bevorzugte Verbindung dieser Erfindung ist), während das (-)-Enantiomere (Verbindung 21) nicht zur Wirkung beisteuert.

Es wurden mit anderen Verbindungfen weitere Versuche unternommen.

Nach der Aufzeichnung von drei reproduzierbaren Miktionszyklen als Vorwert, wurden die Testsubstanzen **24** (1,0; 3,0; 5,0 mg/kg), **25** (1,5 mg/kg) und **26** (3,0 mg/kg) im Vehikel = 0.9 % NaCl i.v. appliziert und die Wirkung auf die cystometrischen Parameter 90 bis 120 Minuten aufgezeichnet. Im Wirkmaximum wurde der Mittelwert von 3 Miktionszyklen bestimmt und als prozentuale Veränderung gegenüber dem Vorwert dargestellt (Tabelle 2).

Tabelle 2:

Verbindung: (Konzentration)	**TP** threshold pressure	**BC** bladder capacity	**ICI** inter-contraction interval
24			
1,0 mg/kg iv (n=7)	+44,0 %***	-8,0 %	-15 %**
3,0 mg/kg iv (n=8)	+94,0 %**	-16,0 %*	-16 %*
5,0 mg/kg iv (n=8)	+69,0 %*	-26,0 %*	-21,2 %
25			
1,5 mg/kg iv (n=8)	+62,0 %*	-14,0 %*	-9,0 %
26			
3,0 mg/kg iv (n=7)	+86,0 %***	+29,0 %*	+27,0 %*

Tabelle 2: Beeinflussung der cystometrischen Parameter durch die Testsubstanzen (Veränderung zum Vorwert [%]); n entspricht der Anzahl der Versuchstiere. Signifikanz (Student T-Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Die untersuchten Substanzen zeigen eine positive Wirkung auf die Blasenregulation und sind somit geeignet zur Behandlung der Harninkontinenz.

Beispiel 3. Testsystem Cystometrie an der narkotisierten naiven Ratte

Die cystometrische Untersuchung an naiven weiblichen Ratten wurde nach der Methode von Kimura et al. (Kimura et al., 1996, Int. J. Urol. 3:218-227) durchgeführt. An narkotisierten, ventilierten Ratten wird das Abdomen eröffnet und die Harnleiter abgebunden. Der Harn wird von den Nieren abgeleitet. Ein Katheter wird in die Blase eingeführt und fixiert. Über diesen wird Saline mittels Infusionspumpe in die Blase infundiert, bis diese rhythmische Spontanaktivität in Form von Kontraktionen zeigt, welche über einen angeschlossenen Druckaufnehmer aufgenommen werden können. Die Testsubstanz wird nach Erreichen stabiler Ausgangswerte in kumulativer Weise i.v. appliziert. Eine Beeinflussung der Blasenfunktion äußert sich über die Unterdrückung der Spontankontraktionen. Dabei gilt als Parameter für die Unterdrückung das Ausbleiben der Kontraktionen über einen Zeitraum von 10 min.

Bei allen hier aufgelisteten Substanzen war eine Unterdrückung der Spontankontraktionen in den Ratten meßbar, wobei Tabelle 3 den Mittelwert der niedrigsten Dosis aus mindestens 2 Versuchen angibt, bei der erstmals Kontraktionen über einen Zeitraum von 10 min ausbleiben.

Tabelle 3: