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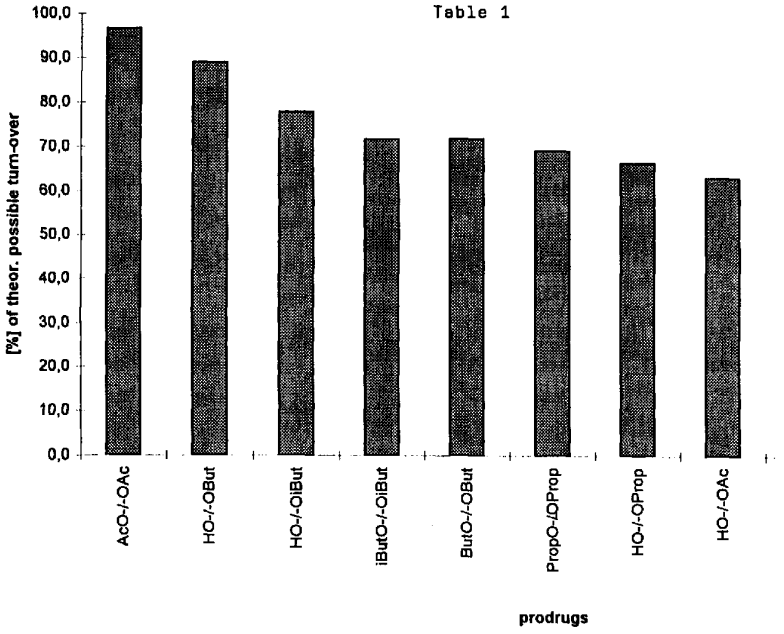
(54) Novel derivatives of 3,3-diphenylpropylamines

(57) The invention concerns 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. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents 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.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



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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. A further object of the invention is to provide novel prodrugs of antimuscarinic agents 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.

[0002] More particularly, the present invention relates to certain prodrugs of 3,3-diphenylpropylamines while avoiding on administration to a mammal a high variation in bioavailability and formation of active metabolites which can result in a substantial variation in response - too low efficacy or too much side effects - for the subjects on the suggested therapy.

[0003] 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 as urinary frequency, urgency and urge incontinence. For this reason antimuscarinic drugs have been instituted as a treatment of bladder over activity.

[0004] 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 over activity. 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 must 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).

[0005] Tolterodine is a new, potent and competetive, 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, Tolderodine - a new bladderselective 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.

[0006] 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 is 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 give a major contribution to the clinical effect in most patients.

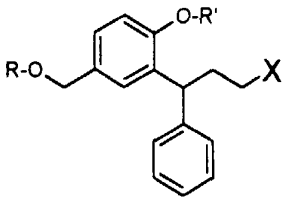
[0007] The document WO 94/11337 discloses that the active metabolite of tolterodine is suggested as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0008] 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. In a method to circumvent this disadvantage different prodrugs of the metabolite have been synthetized and tested for their absorption/bioavailability data.

[0009] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is an 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/bioavailability after oral administration of the drugs or an unfavourable metabolism.

[0010] The novel compounds of the present invention are represented by the general Formula (I)

(I)



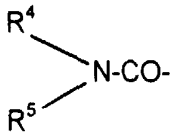
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

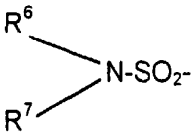
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting



of wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

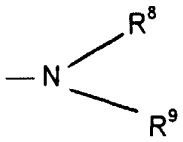
e) a group consisting



of wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

wherein R^8 and R^9 signify 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, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

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.

[0011] The compounds of Formula (I) can form salts with physiologically acceptable acids, organic and inorganic. Furthermore the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid

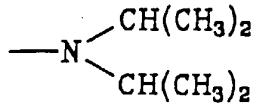
addition salts include the hydrochloride, hydrobromide and the like.

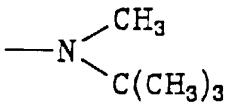
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

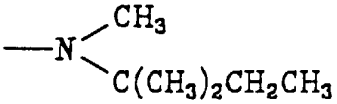
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

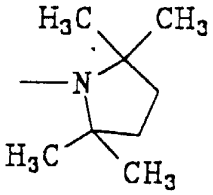
[0014] According to an other embodiment of the invention at least one of R^8 and R^9 comprises a branched carbon chain.

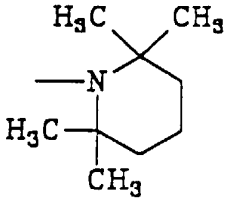
[0015] Presently preferred tertiary amino groups X in Formula I include the following groups a) to h):

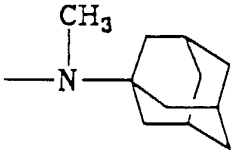
a) 

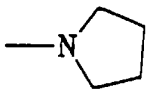
b) 

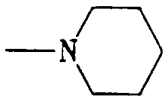
c) 

d) 

e) 

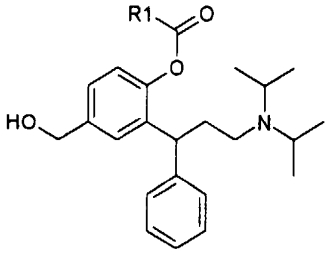
f) 

g) 

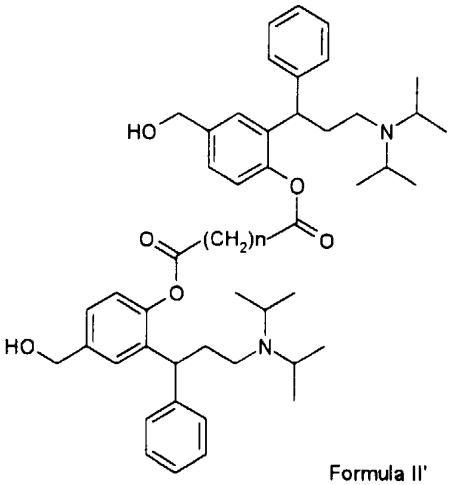
h) 

[0016] Preferred compounds according to the present invention are:

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



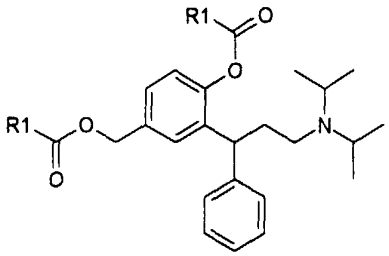
Formula II



Formula II'

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
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Benzoic 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-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester

B) Identical diesters represented by the general Formula III



Formula III

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-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

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