interactions, hydrogen bonds, dipole-dipole interactions, and steric interactions to achieve chiral recognition. To be resolved on a Type I column, analyte enantiomers must contain functionality complementary to that of the CSP so that the analyte undergoes essential interactions with the CSP. The sample should preferably contain one of the following functional groups: p-acid or p-base, hydrogen bond donor and/or acceptor, or an amide dipole. Derivatization is sometimes used to add the interactive sites to those compounds lacking them. The most common derivatives involve the formation of amides from amines and carboxylic acids.

The MetaChiral ODM™ is a type II CSP. The primary mechanisms for the formation of solute-CSP complexes is through attractive interactions, but inclusion complexes also play an important role. Hydrogen bonding, pi-pi, and dipole stacking are important for chiral resolution on the MetaChiral™ ODM. Derivatization is often necessary when the solute molecule does not contain the groups required for solute-column interactions. Derivatization, usually to benzylamides, is also required of some strongly polar molecules like amines and carboxylic acids, which would otherwise interact too strongly with the stationary phase through non-stereo- specific interactions.

The invention provides compounds of formula I as set forth above.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 6436964.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 5585374.

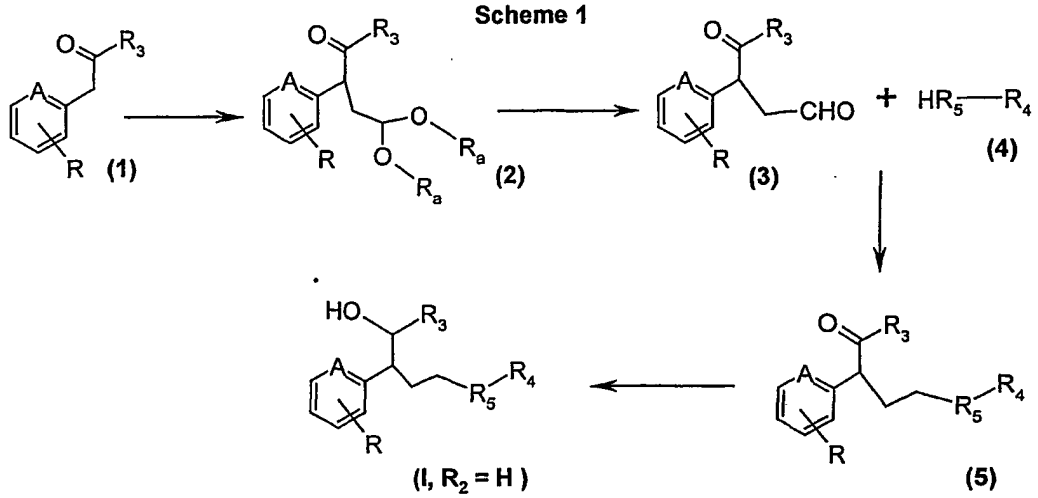
In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formulas disclosed in both US 6436964 and US 5585374.

Compounds of formula I can be separated into diastereomeric pairs by, for example, by separation by TLC.These diastereomeric pairs are referred to herein as diastereoisomer with upper TLC Rf; and diastereoisomer with lower TLC Rf. The diastereoisomers can further be enriched for a particular enantiomer or resolved into a single enantiomer using methods well known in the art , such as those described herein.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

The compounds of the invention are generally prepared according to the following schemes:

Scheme 1



Group R is the same as (R+ R_1) as given in the general formula I. A, R_2, R_3, R_4 and R_5 have the same meanings as given in the general formula I and R_a is a lower alkyl group.

Starting material **(1)** is treated with a base, preferably potassium tert-butoxide, followed by alkylation with 2-bromoacetaldehyde dialkyl acetal or other carbonyl protected 2-haloacetaldehyde (e.g., the R_a alkyl groups can also be joined in a cycle to give a dioxolane or dioxane ring). Other alternative and appropriate bases to carry out the condensation include lithium amides, sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, cesium carbonate and the like with the aid or not of phase transfer catalysts. The reaction is preferably carried out in a solvent such as dimethyl sulfoxide or toluene at a temperature of 0°C to reflux.

The use of 3-bromopropionaldehyde dialkyl acetal or other carbonyl protected 3-halopropionaldehyde allow to obtain, by following the same reaction conditions described above in Scheme 1, compound I having m = 2 as foreseen in the general formula.

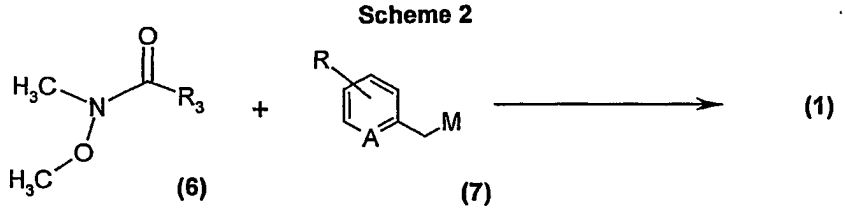
Treatment of **(2)** with an acid, such as hydrochloric acid or p-toluenesulfonic acid or trifluoroacetic acid in a suitable organic solvent, achieves aldehyde **(3)**. Generally, the reaction is conducted in a protic solvent, such a mixture of aqueous acid and acetone or tetrahydrofuran, at temperatures of 5°C to 75°C, preferably at ambient temperature. A preferred similar method consists of carrying out the reaction in a mixture of aqueous trifluoroacetic acid in a chlorinated solvent at r.t.

Aldehyde **(3)** is coupled with the desired amine **(4)** by reductive amination procedure to prepare **(5)**. The reaction is preferably carried out at ambient temperature in

a chlorinated solvent such as dichloroethane or methylene chloride or chloroform in the presence of sodium triacetoxyborohydride and is substantially complete in one to 24 hours (see for example A. F. Abdel-Magid et al., *J. Org. Chem.*, 61, 3849 (1996)) or can be carried out in a protic solvent (e.g., methanol) with the aid of sodium cyanoborohydride, optionally in the presence of molecular sieves.

Reduction of (5) to the alcohol (I) is readily accomplished using a reducing agent such as sodium borohydride or diisobutylaluminum hydride or other aluminum or boron hydride or other reduction method to carry out the conversion ketone to alcohol, well known to those skilled in the art, to prepare the hydroxy compound (I). The reaction is preferably carried out in an organic solvent such as methanol or methylene chloride or tetrahydrofuran at temperatures of -20°C to 0°C - ambient temperature.

Scheme 2



(6) (7)

Starting material (1) is either commercially available or can be prepared by coupling the appropriate Weinreb amide (6) (See Nahm et al., *Tetrahedron Lett.*, 22, 3815, (1981)) with (7), as described in Scheme 2 above, where M is a metallic salt, such as lithium or magnesium halide. The reaction is preferably carried out under nitrogen atmosphere, in an aprotic solvent, such as tetrahydrofuran, at ambient or lower temperatures down to -78°C.

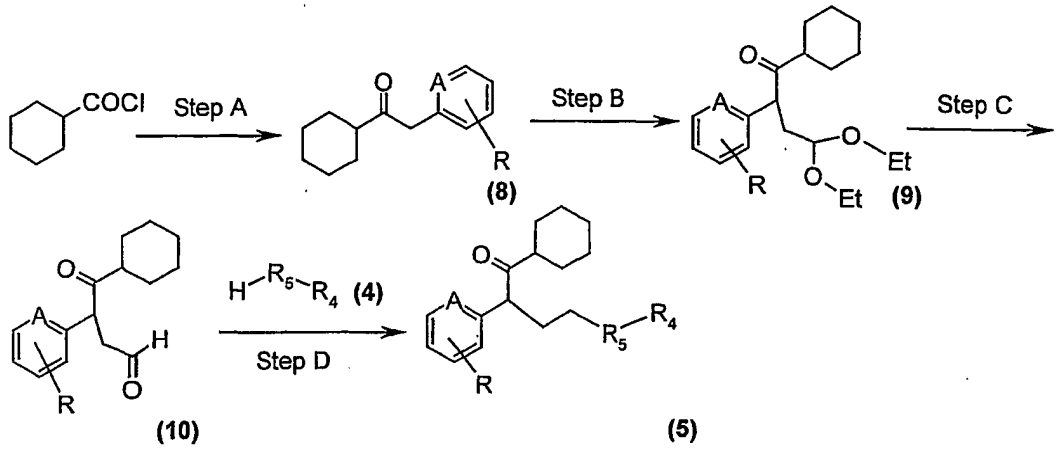
Alternatively, an ester of structure $R_3COOalkyl$ can be treated with a substituted benzylmagnesium chloride or benzylmagnesium bromide or lithium derivative under standard conditions well known in the art to provide the ketone of structure (1).

An alternative route to obtain compounds (1) consists of reacting the appropriate arylaldehyde with an alkylnitro derivative in a nitroaldol fashion, dehydration of the nitro alcohol thus obtained, followed by double bond reduction afford a 2-nitro(2–Ak)phenethyl derivative, which can undergo Nef reaction to yield the wished keto derivative 1. This kind of pathway is well documented in the experimental part and in the literature.

A preferred similar way of synthesis of (1) is the palladium catalysed coupling of an acyl halide with a compound (7) where M is Zn halide. More specifically, the compounds of formula (5) can be prepared following the procedure described in Scheme

3. All substituents, unless otherwise indicated, are as defined previously. The reagents and starting materials are readily available to one of ordinary skill in the art.

Scheme 3



In Scheme 3, step A, for example, cyclohexanecarbonyl chloride is added to a mixture of the suitable benzylzinc chloride(bromide) and an appropriate palladium catalyst, e.g., dichlorobis(triphenylphosphine)palladium (II) stirred at 0°C in a solvent such as tetrahydrofuran. Afterwards, stirring is continued at r.t. for 4-24 h. Then the reaction is quenched for example with an aqueous saturated solution of ammonium chloride. Typical work-up procedure by extraction provides the ketone **(8)**. Ketone **(8)** can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide the purified material. Alternatively, the crude ketone **(8)** can be used in step B without purification.

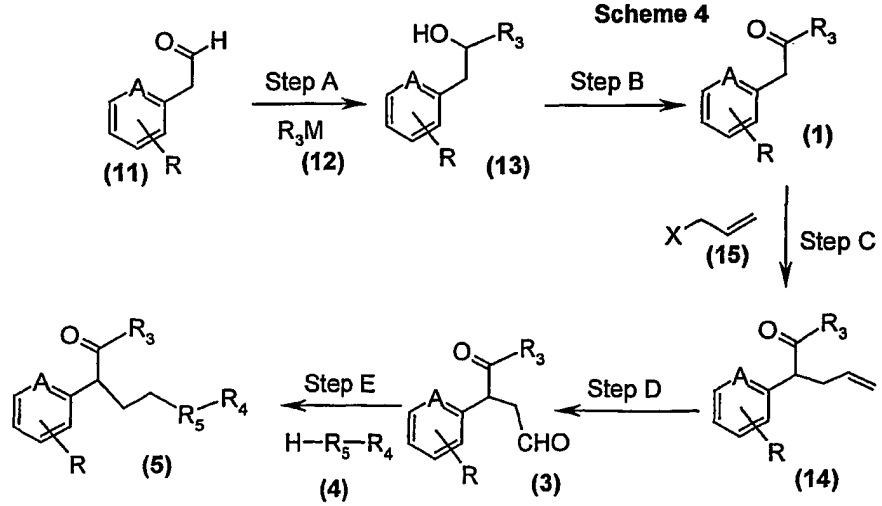
In Scheme 3, step B, ketone **(8)** is alkylated with bromoacetaldehyde diethyl acetal under conditions well known in the art to provide compound of structure **(9)**. For example, ketone **(8)** is dissolved in a suitable organic solvent, such as dimethyl sulfoxide or toluene and treated with a slight excess of a suitable base, such as potassium tert-butoxide. The reaction is stirred for about 15 to 30 minutes at a temperature of between 0°C and the reflux temp. of the solvent and bromoacetaldehyde diethyl acetal is added dropwise to the reaction. One of ordinary skill in the art would readily appreciate that bromoacetaldehyde dimethyl acetal, bromoacetaldehyde ethylene acetal and the like may be used in place of the corresponding diethyl acetal.

In Scheme 3, step C, compound **(9)** is hydrolyzed under acidic conditions to provide aldehyde **(10)** in a manner analogous to the procedure described in Scheme 1. More specifically, for example, compound **(9)** is dissolved in a suitable organic solvent,

such as dichloromethane and treated with a suitable acid, such as aq. trifluoroacetic acid. The reaction mixture is stirred for about 1 to 6 hours at room temperature. The reaction mixture is then diluted with the same solvent, washed with brine; the organic layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide aldehyde (**10**). Aldehyde (**10**) can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane. Alternatively, crude aldehyde (**10**) can be used directly in step D.

In Scheme 3, step D, aldehyde (**10**) is reductively aminated, under conditions well known in the art, with amine (**4**) to provide the ketone (**5**) in a manner analogous to the procedure described in Scheme 1. More specifically, for example, aldehyde (**10**) is dissolved in a suitable organic solvent, such as methylene chloride. To this solution is added about 1.05 or more equivalents of amine (**4**). Acetic acid may optionally be added to aid in dissolution of the amine (**4**). Then about 1.4 to 1.5 equivalents of sodium triacetoxyborohydride is added and the reaction is stirred at room temperature for about 3 to 5 hours. The reaction is then quenched by addition of a suitable base, such as aqueous sodium carbonate or hydroxide to provide a pH from 8 to about 12. The quenched reaction is then extracted with a suitable organic solvent, such as methylene chloride. The organic extracts are combined, washed with brine, dried, filtered and concentrated under vacuum to provide the compound of formula (**5**). This material can then be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/petroleum ether or hexane.

Scheme 4



Alternatively, compounds of structure (**5**) can be prepared following the procedure described in Scheme 4. All substituents, unless otherwise indicated, are previously

defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 4, step A, aldehyde **(11)** is combined with a suitable organometallic reagent **(12)** under conditions well known in the art to provide alcohol **(13)**. Examples of suitable organometallic reagents include Grignard Reagents, alkyl lithium reagents, alkyl zinc reagents, and the like. Grignard Reagents are preferred. For examples of typical Grignard Reagents and reaction conditions, see J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 836-841 (1977). More specifically, aldehyde **(11)** is dissolved in a suitable organic solvent, such as tetrahydrofuran or toluene, cooled to about -5°C and treated with about 1.1 to 1.2 equivalents of a Grignard reagent of formula **(12)** wherein M is MgCl or MgBr. The reaction is stirred for about 0.5 to 6 hours, then quenched, and alcohol **(13)** is isolated by well-known work-up procedure.

In Scheme 4, step B, alcohol **(13)** is oxidized under standard conditions well know in the art, such as those described by J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 1082-1084 (1977), to provide ketone (1). (Ketone (1) is the starting material used in Scheme 1 above.)

For example, the above oxidation is also performed using standard Swern Oxidation conditions which are well known to one of ordinary skill in the art, or the alcohol **(13)** is dissolved in a suitable organic solvent, such as methylene chloride, the solution cooled with a wet ice-acetone bath, and treated with 2.5 to 3.0 equivalents of dimethyl sulfoxide. After stirring for about 30 minutes, the reaction is then treated with about 1.8 equivalents of P_2O_5. The reaction is stirred for about 3 hours and then, preferably, treated over about 30 minutes with about 3.5 equivalents of a suitable amine, such as triethylamine. The cooling bath is then removed and the reaction is stirred for about 8 to 16 hours. The ketone **(1)** is then isolated by standard extraction techniques well known in the art.

In Scheme 4, step C, ketone **(1)** is treated with a suitable base followed by addition of the alkene **(15)**, wherein X is a suitable leaving group, to provide compound **(14)**. For example, ketone **(1)** is combined with an excess of alkene **(15)** in a suitable organic solvent, such as tetrahydrofuran, and cooled with a wet ice acetone bath. Examples of suitable leaving groups are Cl, Br, I, tosylate, mesylate, and the like. Preferred leaving groups are Cl and Br. About 1.1 equivalents of a suitable base are added and the reaction is allowed to stir for about 2 hours at room temperature. Examples of

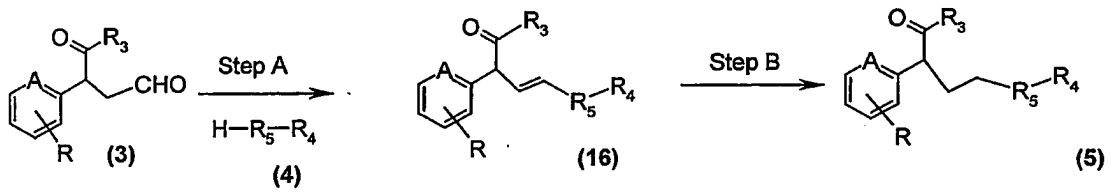
suitable bases are potassium tert-butoxide, sodium hydride, $NaN(Si(CH_3)_3)_2$, LDA, $KN(Si(CH_3)_3)_2$, $NaNH_2$, sodium ethoxide, sodium methoxide and the like. Potassium tert-butoxide is the preferred suitable base. The reaction is then quenched with aqueous acid and compound **(14)** is isolated by usual work-up procedure.

In Scheme 4, step D, compound **(14)** is treated with a suitable oxidizing agent to provide aldehyde **(3)**. (Aldehyde **(3)** is also prepared in Scheme 1.) Examples of suitable oxidizing agents are ozone, $NaIO_4$ /Osmium catalyst, and the like. Ozone is the preferred oxidizing agent. Examples of suitable oxidizing reagents and conditions are described by J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 1090-1096 (1977).

For example, compound **(14)** is dissolved in a suitable organic solvent, such as methanol, a small amount of Sudan III is added, and the solution is cooled to about -20°C. Ozone is bubbled into the solution for about 4 hours until the pink color turns to a pale yellow color. Then a reducing agent such as Me_2S or tributylphosphine is added. Concentration provides the intermediate dimethyl acetal of aldehyde **(3)**. This dimethyl acetal is readily hydrolyzed under standard acidic conditions to provide aldehyde **(3)**. Alternatively, direct acidic work-up of the crude reaction mixture provides aldehyde **(3)**. Alternatively, aldehyde **(3)** can be obtained directly by ozonolysis of **(14)** in a non-acetal forming solvent, such as methylene chloride.

In Scheme 4, step E, aldehyde **(3)** is reductively aminated under conditions analogous to those described above in Scheme 3, step D, to provide compound **(5)**. (Compound **5** is also prepared in Scheme 1.)

Scheme 5



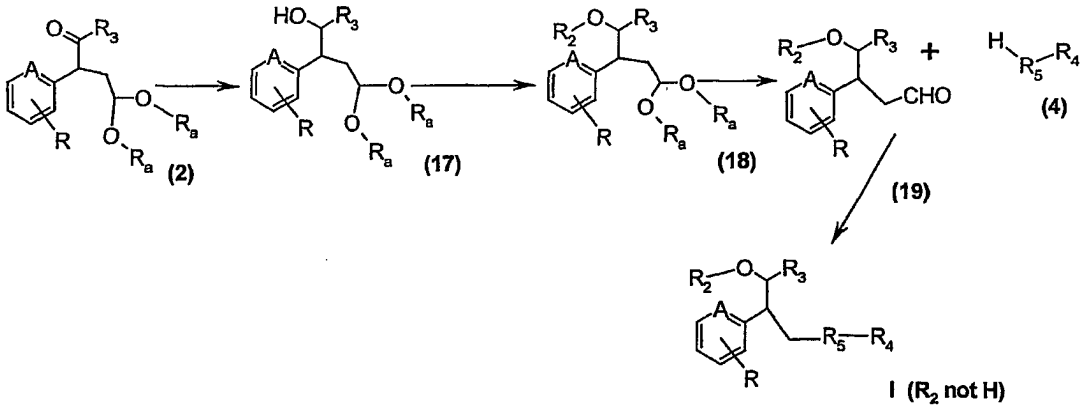
Scheme 5 provides an alternative synthesis for the preparation of ketone **(5)**. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 5, step A, aldehyde **(3)** is condensed with amine **(4)** under standard conditions well known in the art to provide the enamine **(16)**. For example, about 1.05 equivalents of aldehyde **(3)** dissolved in a suitable organic solvent, such as isopropyl

acetate or isopropanol, is added to neat amine **(4)**, free base. Additional organic solvent is added to produce a slurry and the reaction is stirred for about 1 to 2 hours. The enamine **(16)** is then isolated by standard techniques, such as collection by filtration.

In Scheme 5, step B, the enamine **(16)** is hydrogenated under conditions well known to one of ordinary skill in the art to provide compound **(5)**. For example, enamine **(16)** is combined with a suitable organic solvent, such as isopropyl alcohol and a catalytic amount of 5% palladium on carbon in a Parr bottle. The mixture is placed under 50 psi of hydrogen and shaken for about 2 days at room temperature. The slurry is then filtered to remove catalyst and the filtrate is concentrated to provide compound **(5)**.

Scheme 6

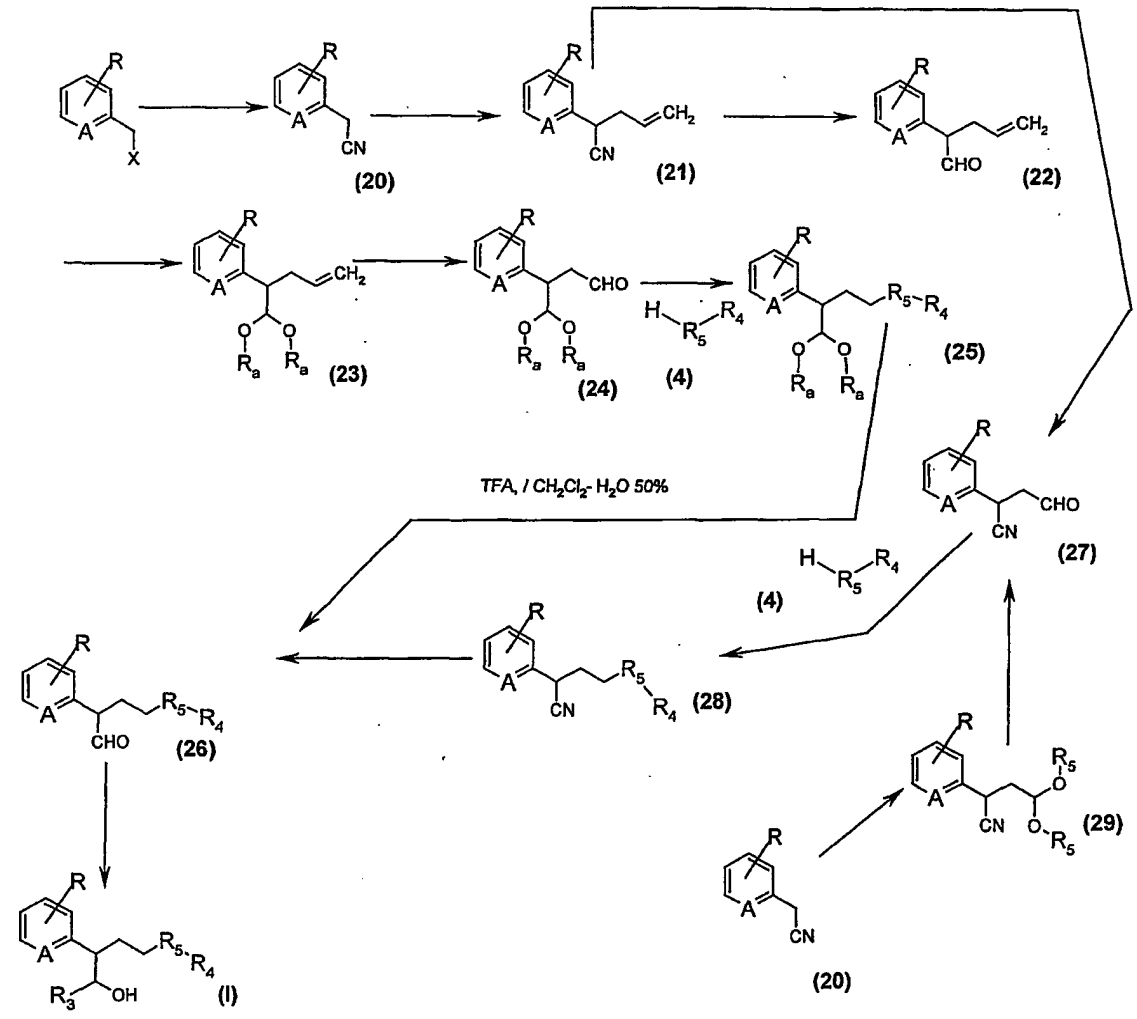


For the synthesis of compounds I where R_2 is different than H, the method given in Scheme 6 is used. Intermediate ketone **(2)** is reduced with the same reduction methods used above in scheme 1 for compound **(5)** affording intermediate **(17)**, which is etherified by reaction with a base, for example NaH or potassium tert-butoxide or $NaNH_2$ or $LiNH_2$ or others in a suitable solvent e.g. tetrahydrofuran, affording the alkoxide, which is then reacted in situ with the appropriate R_2-X with X leaving group (halogen or mesylate or tosylate) at a temperature of from 0°C to the reflux temperature. The so obtained compounds **(18)** can undergo the same reactions described in scheme 1 affording product **I** with R_2 is not H.

Alternatively, compounds of formula I where R_2 is not a hydrogen atom, can be obtained by alkylating compounds of formula I where R_2 = H with the same methods described above for alkylating compound **17**, limiting this procedure to the alkylation with very reactive halogenide or mesylate/tosylate (e.g., benzyl bromides) which can react under time/temperature controlled reaction condition, preferably at r.t.

Scheme 7 describes a double functionalization approach to the synthesis of Compound (I). This kind of approach can be useful for the synthesis of libraries of compounds (I) introducing different amine moieties and different R_3 goups at the same time.

Scheme 7



In scheme 7 R_a is a lower alkyl group or the two R_a groups are linked forming a 1,3-dioxolanyl or 1,3-dioxanyl group. An appropriate commercial benzyl derivative (with X = halogen or methanesulphonyloxy or p-toluenesulphonyloxy groups) can be reacted, as very well known to those skilled in the art, to afford the benzyl cyanide (20). These reactants can be converted following known alkylation methods into compounds

(21) or (27) respectively reacting them with allyl halogenides (or allyl mesylatese or tosylates) or haloalkylaldehydes in their carbonyl protected form (acetals or dioxolanyl derivatives or other).

These alkylation reactions can be carried out by the use of bases to generate the reactive benzyl carbanions. Example of used bases are lithium diisopropylamide (LDA) or tert-Butyl lithium or NaH or potassium tert-butoxide or sodium amide or potassium amide or others in an appropriate solvent such as THF or Et_2O or DMF or other at a temperature ranging from –78°C to the reflux temperature. A preferred method of alkylation include the use of hindered bases such as LDA in the presence of hexamethyl phosphorous triamide or DMPU at –78°C – r.t.

Compounds (21) can be in turn reduced by the use of diisobutylaluminum hydride (DIBAL-H) in an appropriate solvent (toluene, DMF, CH_2Cl_2 or other) at a temperature ranging from –78°C to the reflux of the solvent. The so obtained aldehydes (22) are then carbonyl protected following methods very well known to those skilled in the art to give compounds (23), which can be catalytically osmilated (C. P. Forbes *J.C.S. Perkin Trans I* 1979, 906-910) or undergo ozonolysis to afford compounds (24). Compounds (24) can be reductively aminated as described above to afford compounds (25). Deprotection by common methods leads to the aldehydes (26).

Compounds (26) can be alternatively obtained from compounds (21) applying the osmilation or ozonolysis procedure on them. The so obtained cyanopropionaldehydes (27) are then reductively aminated to compound (28). Repeating the DIBAL-H reduction described above on these compounds affords the aldehydes (26).

Compounds (27) are also easily obtained from compounds (29) by simple deprotection of the carbonyl functionality. The reaction of R_3-M (where M is a metallic salt, such as lithium or magnesium halide) with compounds (26) afford compounds (I). A large number of organometallics such as litium or magnesium derivatives are commercially available or easily prepared and can be reacted in an appropriate solvent such as THF or Et_2O or others at –78°C – reflux.

Stereochemistry

In Schemes 1, 6 and 7 compounds I are obtained in syn/anti mixture of diastereoisomers with ratio depending on the reaction condition used. The diastereoisomers can be separated by usual tecniques known to those skilled in the art

including fractional crystallization of the bases or their salts or chromatografic tecniques such as LC or flash chromatography. For both the diastereoisomers, the (+) enantiomer of formula Ia can be separated from the (-) enantiomer using techniques and procedures well known in the art, such as that described by J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981. For example, chiral chromatography with a suitable organic solvent, such as ethanol/acetonitrile and Chiralpak AD packing, 20 micron can also be utilized to effect separation of the enantiomers.

The free bases of formula I, their diastereoisomers or enantiomers can be converted to the corresponding pharmaceutically acceptable salts under standard conditions well known in the art. For example, the free base of formula I is dissolved in a suitable organic solvent, such as methanol, treated with one equivalent of maleic or oxalic acid for example, one or two equivalents of hydrochloric acid or methanesulphonic acid for example, and then concentrated under vacuum to provide the corresponding pharmaceutically acceptable salt. The residue can then be purified by recrystallization from a suitable organic solvent or organic solvent mixture, such as methanol/diethyl ether.

Combination treatments

In certain embodiments, disorders of the urinary tract are treated by administering a compound of formula I in combination with an additional 5-HT_{1A} antagonist or an antagonist of one or more additional class of receptors. In preferred embodiments a compound of formula I is administered in combination with an antagonist of an α1-adrenergic, or muscarinic receptor.

In further embodiments, lower urinary tract disease is treated by administering a compound of formula I in combination with one or more inhibitor of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

Examples of antimuscarinic drugs for administration in combination with a compound of formula I are oxybutynin, tolterodine, darifenacin, and temiverine.

A compound of formula I may be administered in combination with α1-adrenergic antagonists, for the therapy of lower urinary tract symptoms, whether or not these are associated with BPH. Preferred α1-adrenergic antagonists suitable for administration in combination with a compound of formula I are, for example, prazosin, doxazosin,

terazosin, alfuzosin, and tamsulosin. Additional α1-adrenergic antagonists suitable for administration in combination with a compound of formula I are described in U.S. Patents No. 5,798,362, 5,990,114; 6,306,861; 6,365,591; 6,387,909; and 6,403,594.

Examples of 5-HT_{1A} antagonists that may be administered in combination with a compound of formula I are found in Leonardi et al., *J. Pharmacol. Exp. Ther.* **299**: 1027-1037, 2001 (e.g., Rec 15/3079), U.S. Patent No. 6,071,920, other phenylpiperazine derivatives described in WO 99/06383 and pending U.S. Patent Applications Serial No. 10/266,088 and 10/266,104 filed on October 7, 2002. Additional 5-HT_{1A} antagonists include DU-125530 and related compounds described in U.S. Patent No. 5,462,942 and robalzotan and related compounds described in WO 95/11891.

Examples of selective COX2 inhibitors that may be administered in combination with a compound of formula I are, without limitation, nimesulide, meloxicam, rofecoxib, celecoxib, parecoxib and valdecoxib. Additional examples of selective COX2 inhibitors are described, without limitation, in US 6,440,963. Examples of non-selective COX1-COX2 inhibitors are, without limitation, acetylsalicylic acid, niflumic acid, flufenamic acid, enfenamic acid, meclofenamic acid, tolfenamic acid, thiaprophenic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, furprofen, indomethacin, acemethacin, proglumethacin, ketorolac, diclofenac, etodolac, sulindac, fentiazac, tenoxicam, lornoxicam, cynnoxicam, ibuproxam, nabumetone, tolmetin, amtolmetin. Accordingly, each of the foregoing are non-limiting examples of COX inhibitors that may be administered in combination with a compound of formula I.

Examples of derivatives of COX inhibitors that may be administered in combination with a compound of formula I are derivatives of COX inhibitors bearing nitrate (nitrooxy) or nitrite groups, such as those given , for example, in WO 98/09948, able to release NO in vivo.

Pharmaceutical Compositions

The invention further provides pharmaceutical compositions comprising a compound of formula I or an enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or pharmaceutically acceptable salt of the compound. The pharmaceutical composition may also include optional additives, such as a pharmaceutically acceptable carrier or diluent, a flavouring, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrator, an excipient, a diluent, a lubricant, an absorption enhancer, a bactericide and the like, a

stabiliser, a plasticizer, an edible oil, or any combination of two or more of said additives.

Suitable pharmaceutically acceptable carriers or diluents include, but are not limited to, ethanol, water, glycerol, aloe vera gel, allantoin, glycerine, vitamin-A and E oils, mineral oil, phosphate buffered saline, PPG2 myristyl propionate, magnesium carbonate, potassium phosphate, vegetable oil, animal oil and solketal.

Suitable binders include, but are not limited to, starch, gelatine, natural sugars such as glucose, sucrose and lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, vegetable gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Suitable disintegrators include, but are not limited to, starch such as corn starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Suitable suspending agents include, but are not limited to, bentonite.

Suitable dispersing and suspending agents include, but are not limited to, synthetic and natural gums such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone and gelatine.

Suitable edible oils include, but are not limited to, cottonseed oil, sesame oil, coconut oil and peanut oil.

Examples of additional additives include, but are not limited to, sorbitol, talc, stearic acid and dicalcium phosphate.

Unit Dosage Forms

The pharmaceutical composition may be formulated as unit dosage forms, such as tablets, pills, capsules, boluses, powders, granules, sterile parenteral solutions, sterile parenteral suspensions, sterile parenteral emulsions, elixirs, tinctures, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories. The unit dosage forms may be used for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation, transdermal patches, and a lyophilized composition. In general, any delivery of active ingredients that results in systemic availability of such ingredients can be used. Preferably the unit dosage form is an oral dosage form, most preferably a solid oral dosage; therefore the preferred dosage forms are tablets, pills and capsules. However, parenteral preparations are preferred too.

Solid unit dosage forms may be prepared by mixing the active agents of the present invention with a pharmaceutically acceptable carrier and any other desired

additives as described above. The mixture is typically mixed until a homogeneous mixture of the active agents of the present invention is obtained and the carrier and any other desired additives are formed, i.e. the active agents are dispersed evenly throughout the composition. In this case, the composition can be formed as dry or moist granules.

Dosage forms can be formulated as, for example, "immediate release" dosage forms. "Immediate release" dosage forms are typically formulated as tablets that release at least 60%-90% of the active ingredient within 30-60 min when tested in a drug dissolution test, e.g., U.S. Pharmacopeia standard <711>. In a preferred embodiment, immediate dosage forms release at 75% of active ingredient within about 45 min.

Dosage forms can also be formulated as, for example, "controlled release" dosage forms. "Controlled," "sustained," "extended" or "time release" dosage forms are equivalent terms that describe the type of active agent delivery that occurs when the active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, which is generally on the order of minutes, hours or days, typically ranging from about sixty minutes to about 3 days, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid. A controlled release rate can vary as a function of a multiplicity of factors. Factors influencing the rate of delivery in controlled release include the particle size, composition, porosity, charge structure, and degree of hydration of the delivery vehicle and the active ingredient(s), the acidity of the environment (either internal or external to the delivery vehicle), and the solubility of the active agent in the physiological environment, i.e., the particular location along the digestive tract. Typical parameters for dissolution test of controlled release forms are found in U.S. Pharmacopeia standard <724>.

Dosage forms can also be formulated to deliver active agent in multiphasic stages whereby a first fraction of an active ingredient is released at a first rate and at least a second fractions of active ingredient is released at a second rate. In a preferred embodiment, a dosage form can be formulated to deliver active agent in a biphasic manner, comprising a first "immediate release phase", wherein a fraction of active ingredient is delivered at a rate set forth above for immediate release dosage forms, and a second "controlled release phase," wherein the remainder of the active ingredient is released in a controlled release manner, as set forth above for controlled release dosage forms.

Tablets or pills can be coated or otherwise prepared so as to form a unit dosage

form that has delayed and/or sustained action, such as controlled release and delayed release unit dosage forms. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of a layer or envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release.

Biodegradable polymers for controlling the release of the active agents include, but are not limited to, polylactic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

For liquid dosage forms, the active substances or their physiologically acceptable salts are dissolved, suspended or emulsified, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. Solvents for the active combinations and the corresponding physiologically acceptable salts can include water, physiological salt solutions or alcohols, e.g. ethanol, propanediol or glycerol. Additionally, sugar solutions such as glucose or mannitol solutions may be used. A mixture of the various solvents mentioned may be used in the present invention too.

A transdermal dosage form is contemplated by the present invention too. Transdermal forms may be a diffusion transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery systems. Transdermal dosage forms may be used for delayed release and sustained release of the active agents of the present invention.

The pharmaceutical compositions and unit dosage forms of the present invention for parenteral administration, and in particular by injection, typically include a pharmaceutically acceptable carrier, as described above. A preferred liquid carrier is vegetable oil. Injection may be, for example, intravenous, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous.

The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active agents of the present invention may also be coupled with soluble

polymers such as targetable drug carriers. Such polymers include, but are not limited to, polyvinylpyrrolidone, pyran copolymers, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol, and polyethylenoxypolylysine substituted with palmitoyl residues.

Administration

The pharmaceutical composition or unit dosage forms of the present invention may be administered by a variety of routes, such as the oral and enteral, intravenous, intramuscular subcutaneous, transdermal, transmucosal (including rectal and buccal) and by inhalation routes. Oral or transdermal routes are preferred (e.g., solid or liquid formulations or skin patches, respectively).

The pharmaceutical composition or unit dosage forms comprising an effective amount of the present invention may be administered to an animal, preferably a human, in need of treatment of neuromuscular dysfunction of the lower urinary tract described by E. J. McGuire in "Campbell's UROLOGY", 5th Ed., 616-638, 1986, W.B. Saunders Company, and patients affected by any physiological dysfunction related to impairment of 5-HT_{1A} receptor function. Such dysfunctions include, without limitation, central-nervous-system disorders such as depression, anxiety, eating disorders, sexual dysfunction, addiction and related problems.

As used herein, the term "effective amount" refers to an amount that results in measurable amelioration of at least one symptom or parameter of a specific disorder. In a preferred embodiment, the compound treats disorders of the urinary tract, such as urinary urgency, overactive bladder, increased urinary frequency, reduced urinary compliance (reduced bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder, or central nervous system disorders due to serotonergic dysfunction (such as anxiety, depression, hypertension, sleep/wake cycle disorders, feeding behaviour, sexual function and cognition disorders in mammals (particularly a human) associated to stroke, injury, dementia and due to neurological development, disorders from hyperactivity related to an attention deficit (ADHD), drug addiction, drug withdrawal, irritable bowel syndrome.

The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimising toxicity or side effects for a particular patient. However, such fine tuning of the therapeutic regimen is routine in the light of the guidelines given herein.

The dosage of the active agents of the present invention may vary according to a variety of factors such as underlying disease conditions, the individual's condition, weight, sex and age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art, for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician. It will be understood that any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination or both, and these may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present method of treatment.

The amount of the agent to be administered can range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the present invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, the compounds are formulated in capsules or tablets, preferably containing 50 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 50 to 400 mg, preferably 150 to 250 mg and most preferably about 200 mg, for relief of urinary incontinence and dysfunctions under treatment with 5-HT_{1A} receptor ligand.

A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the present invention, based upon 100% weight of total pharmaceutical composition.

Generally, transdermal dosage forms contain from about 0.01% to about 100% by

weight of the active agents versus 100% total weight of the dosage form.

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. For example, the compounds of the invention may be administered in combination with more antimuscarinic, α_1-adrenergic antagonist, 5-HT_{1A} receptor antagonist, or COX inhibitors or NO releasing derivatives thereof, for the therapy of lower urinary tract symptoms. Examples of antimuscarinics, α_1-adrenergic antagonists, 5-HT_{1A} receptor antagonist, COX inhibitors and NO releasing derivatives thereof are set forth above, without limitation.

For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at separate staggered times. For example, the compound of the invention may be administered in the morning and the antimuscarinic compound may be administered in the evening, or vice versa. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, sex and medical condition of the patient; the severity and aetiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

Uses-Methods for Treatment

Without wishing to be bound by theory, it is believed that administration of 5-HT_{1A} receptor antagonists prevents unwanted activity of the sacral reflex and/or cortical mechanisms that control micturition. Thus, it is contemplated that a wide range of neuromuscular dysfunctions of the lower urinary tract can be treated using the compounds of the present invention, including without limitation dysuria, incontinence and enuresis (overactive bladder). Dysuria includes urinary frequency, nocturia, urgency, reduced urinary compliance (reduced bladder storage capacity), difficulty in emptying the bladder, i.e. a suboptimal volume of urine is expelled during micturition. Incontinence syndromes include stress incontinence, urgency incontinence and enuresis incontinence, as well as mixed forms of incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

The compounds of the present invention may also be useful for the treatment of central nervous system disorders due to serotonergic dysfunction.

The following examples represent typical syntheses of the compounds of formula I as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Example 1

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

2-(2-Cyclohexyl-2-oxoethyl)-benzonitrile (Compound 1a)

To a solution of 0.47 g of 2-tolunitrile in 4 ml of THF was added 0.535 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU) and the mixture was cooled at –78°C; 2.22 ml of a 2M sol. of LDA in THF was then dropped during 5 min., then the reaction mixture was stirred at the same temperature for 15 min. followed by dropwise addition of 0.757 g of N-methyl-N-methoxycyclohexanecarboxamide in 4 ml of THF. After 1 h stirring at –78°C, the reaction mixture was quenched with a 10% aq. sol. of NH_4Cl. The temperature was allowed to rise at r.t. and the mixture was extracted with EtOAc (2x20ml), washed with 30 ml of brine, dried on Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash chromatography (PE – EtOAc 90:10) to afford 0.34 g of the title compound.

^{1}H-NMR (*$CDCl_3$, δ*): 1.10-2.05 (m ,10H); 2.45-2.60 (m, 1H); 4,00 (m, 2H); 7.20-7.43 (m, 2H); 7.48-7.70 (m, 2H);

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde diethyl acetal (Compound 1b)

To a suspension of 414 mg of 60% NaH oil dispersion in 10 ml of anhydrous DMF was added drop wise during 6 min under a nitrogen stream, a solution of 1.84 g of compound 1a in 5 ml of DMF and the reaction mixture was stirred at r.t. for 1 h; then was added 2.15 g of 2-bromoacetaldehyde diethyl acetal (97 %) in 5 ml of DMF; the mixture was stirred at r.t. for 15', then at 80°C for 5.5 h. Afterwards, the mixture was diluted with H_2O (250 ml), acidified with 2 N HCl, extracted with Et_2O (3 x 50 ml), washed with H_2O (40 ml), dried (Na_2SO_4) ed evaporated in vacuo, affording a crude (brownish oil), which was

purified by flash chromatography (PE - EtOAc 90:10) to yield 1.91 g of compound 1b as a yellowish oil.

^{1}H-NMR (*CDCl$_3$, δ*): 1.09-1.26 (m, 6H); 1.27-1.39 (m, 4H); 1.46-1.57 (m, 1H); 1.59-1.74 (m, 3H); 1.77-1.88 (m, 1H); 1.93-2.08 (m, 2H); 2.38-2.50 (m, 2H); 3.39-3.51 (m, 2H); 3.54-3.72 (m, 2H); 4.30-4.34 (m, 1H); 4.53-4.61 (m, 1H); 7.33-7.44 (m, 2H); 7.51-7.61 (m, 1H); 7.66-7.72 (m, 1H).

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde (Compound 1c)

A mixture of 1 g of the compound 1b, 9.5 ml of 50% aq. trifluoroacetic acid and 19 ml of CH_2Cl_2 was stirred for 2 h at r.t., then diluted with 8 ml of CH_2Cl_2. The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo to afford a crude (0.788 g), used in the next step without further purification.

^{1}H-NMR (*CDCl$_3$, δ*): 1.01-2.11 (m, 10H); 2.31-2.43 (m, 1H); 2.64 (dd, 1H); 3.29-3.41 (m, 1H); 4.78 (dd, 1H); 7.25-7.37 (m, 1H); 7.39-7.53 (m, 2H); 7.61-7.64 (m, 1H); 9.62-9.68 (m, 1H).

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

A mixture of 0.197 g of the compound 1c, 0.177 g of 8-(N-methyl-2-aminoethoxy)-quinoline, 0.31 g of sodium triacetoxyborohydride, 0.17 ml of AcOH and 6 ml of CH_2Cl_2 was stirred at r.t. for 1 h and alkalinised with 2 N NaOH. The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo the give a crude which was purified by flash chromatography (CH_2Cl_2 - MeOH 95:5) affording the title compound (0.17 g; 52%).

^{1}H-NMR (*CDCl$_3$, δ*): 1.11-1.40 (m, 5H); 1.51-1.60 (m, 1H); 1.61-1.83 (m, 6H); 1.85-2.02 (m, 2H); 2.30-2.52 (m, 5H); 2.95-3.08 (m, 2H); 4.26-4.38 (m, 2H); 4.50-4.61 (m, 1H); 7.11 (d, 1H); 7.32-7.38 (m, 1H); 7.39-7.57 (m, 4H); 7.67 (d, 1H); 8.15 (d, 1H); 8.92-8.99 (m, 1H).

$[M+H]^+ = 456.25$

Example 2

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline

To a solution of 0.17 g of Compound of Example 1 in MeOH (5 ml), cooled at 0°C, 21.2 mg of $NaBH_4$ were added; the resulting mixture was stirred at 0°C for 30', then 1 h at r.t. Afterwards, the solvent was evaporated in vacuo and the crude poured into H_2O (10 ml) and extracted with CH_2Cl_2 (3x10 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness in vacuo. The crude was purified by flash chromatography (EtOAc – 2 N methanolic ammonia 97:3) affording the title compound (55 mg; 32%).
$[M+H]^+ = 458.42$

Example 3

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(2,6-dimethylphenyl)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (CH_2Cl_2 – MeOH 97:3) yielded the title compound (32.8%) as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).
$[M+H]^+ = 443.33$

Example 4

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 2, but using the compound of Example 3 as starting material instead of the compound of Example 1. Purification by flash chromatography (CH_2Cl_2 - MeOH / NH_3 97:3) yielded the title compound (20.9%) as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).
$[M+H]^+ = 445.44$

Example 5

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(4-fluoro-2-methoxyphenoxy)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (EP - EtOAc - MeOH / NH_3 7:3:0.2) yielded the title compound (12.3%)as an oil.
^{1}H-NMR (*$CDCl_3$, δ*): 1.06-1.33 (m, 5H), 1.41-2.90 (m, 16H), 2.58-2.76 (m, 2H), 3.74 (s, 3H); 3.98-4.11 (m, 1H), 4.89-4.54 (m, 1H), 6.43-6.52 (m, 1H); 6.54-6.60 (m, 1H); 6.73-6.81 (m, 1H); 7.22-7.33 (m, 1H); 7.35-7.53 (m, 2H); 7.57-7.69 (m, 1H).
$[M+H]^+ = 479.29$

Example 6 Radioligand binding to recombinant 5-HT_{1A} receptors

A. Method:

A Genomic clone G-21 coding for the human $5HT_{1A}$-serotonergic receptor is stably transfected in a human cell line (HeLa). HeLa cells are grown as monolayers in Dulbecco's modified Eagle medium (DMEM), containing 10% foetal bovine serum, gentamycin (0.1 mg/ml) and 5% carbon dioxide, at 37°C. The cells are detached from the growth flask at 95% confluence by a cell scraper and are lysed in cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4). The homogenates are centrifuged at 40000 x *g* x 20 minutes and the pellets are resuspended in a small volume of cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4) and immediately frozen and stored at –70°C until use. On the day of experiment, the cell membranes are resuspended in incubation buffer: 50 mM Tris HCl (pH 7.4), 2.5 mM $MgCl_2$, 10 mM pargyline (Fargin et al., *Nature* **335**, 358-360, 1988). The membranes are incubated in a final volume of 1 ml for 30 minutes at 30°C with 1 nM [^{3}H]8-OH-DPAT, in the absence or presence of the test compounds. Non-specific binding is determined in the presence of 10 µM 5-HT. Incubation is stopped by addition of cold Tris-HCl buffer and rapid filtration through a 0.2%-polyethyleneimine-pretreated Whatman-GF/B or Schleicher-&-Schuell-GF52 filter.

B. Results

The affinity of the tested compounds is evaluated as inhibition of specific binding

of the radioligand to 5-HT_{1A} receptors (IC_{50}) by using the non-linear curve-fitting program Allfit (De Lean et al., *Am. J. Physiol.* 235, E97-E102 (1978). The IC_{50} value is converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (Cheng Y. C., et al., *Biochem. Pharmacol.* 22, 3099-3108 (1973)).

Example 7 Effects on rhythmic bladder-voiding contractions induced by bladder filling in anaesthetised rats

A. Method:

Female Sprague-Dawley rats weighing 225-275 g (Crl: CD® (SD) IGS BR, Charles River Italia) are used. The animals are housed with free access to food and water and maintained on a forced 12-hour alternating light-dark cycle at 22-24°C for at least one week, except during the experiment. The activity on rhythmic bladder voiding contractions is evaluated according to the method of Dray (Dray J., *Pharmacol. Methods*, 13:157, 1985), with some modifications as in Guarneri (Guarneri, *Pharmacol. Res.* 27:173, 1993). Briefly, the rats are anaesthetised by subcutaneous injection of 1.25 g/kg (5 ml/kg) urethane, after which the urinary bladder is catheterised via the urethra using PE 50 polyethylene tubing filled with physiological saline. The catheter is tied in place with a ligature around the external urethral orifice and is connected to conventional pressure transducers (Statham P23 ID/P23 XL). The intravesical pressure is displayed continuously on a chart recorder (Battaglia Rangoni KV 135 with DCI/TI amplifier). The bladder is then filled via the recording catheter by incremental volumes of warm (37°C) saline until reflex bladder-voiding contractions occurred (usually 0.8-1.5 ml). For intravenous injection of bioactive compounds, PE 50 polyethylene tubing filled with physiological saline is inserted into the jugular vein.

From the cystometrogram, the number of contractions recorded 15 minutes before (basal values) and after treatment, as well as the mean amplitude of these contractions (mean height of the peaks in mmHg), is evaluated.

Since most compounds produce an effect that is relatively rapid in onset and leads to a complete cessation of bladder contractions, bioactivity is conveniently estimated by measuring the duration of bladder quiescence (i.e., the length of the time during which no contractions occurred). The number of tested animals showing a reduction in the number of contractions higher than 30% of that observed in the basal period is also recorded.

To compare the potency of tested compounds for inhibiting the bladder voiding

contractions, equieffective doses which result in the disappearance of contractions for a time of 10 minutes (ED_{10min}) are computed by means of linear regression using the least square method. The extrapolated doses which induce a reduction in the number of contractions greater than 30% in 50% of the treated rats (ED_{50}) is evaluated by the method of Bliss (Bliss C. I., *Quart J. Pharm. Pharmacol.* 11, 192-216, 1938).

B. Results

The rapid distension of the urinary bladder in urethane-anaesthetised rats produces a series of rhythmic bladder-voiding contractions whose characteristics have been described (Maggi et al., *Brain Res.* 380:83, 1986; Maggi et al., *J. Pharmacol. Exp. Ther.*, 230: 500, 1984). The frequency of these contractions is related to the sensory afferent arm of reflex micturition and to the integrity of the micturition centre, while their amplitude depends on the function of the reflex efferent arm. In this model system, compounds that act mainly on the central nervous system (such as morphine) cause a block in voiding contractions, whereas drugs that act at the level of the detrusor muscle, such as oxybutynin, lower the amplitude of the bladder contractions.

Example 8 Effect on cystometric parameters in conscious rats after oral administration

A. Method:

Male Sprague-Dawley rats [Crl: CD® (SD) IGS BR] of 300-400 g supplied by Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature, except during the experiment. To quantify urodynamic parameters in conscious rats, cystometrographic studies is performed according to the procedure previously reported (Guarneri et al., *Pharmacol. Res.* 24: 175, 1991).

Briefly, the rats are anaesthetised by intraperitoneal administration of 3 ml/kg of Equithensin solution (pentobarbital 30 mg/kg and chloral hydrate 125 mg/kg) and placed in a supine position. An approximately-10-mm-long midline incision is made in the shaved and cleaned abdominal wall. The urinary bladder is gently freed from adhering tissues, emptied and then cannulated via an incision in the bladder body, using a polyethylene cannula (0.58-mm internal diameter, 0.96-mm external diameter) which is permanently sutured with silk thread. The cannula is exteriorised through a subcutaneous

tunnel in the retroscapular area, where it is connected to a plastic adapter in order to avoid the risk of removal by the animal. For drug testing, the rats are utilised one day after implantation.

On the day of the experiment, rats are placed in modified Bollman cages, i.e., restraining cages, that are large enough to permit the rats to adopt a normal crouched posture, but narrow enough to prevent turning around. After a stabilisation period of about 20 minutes, the free tip of the bladder cannula is connected through a T-shaped tube to a pressure transducer (Statham P23XL) and to a peristaltic pump (Gilson minipuls 2) for continuos infusion of a warm (37°C) saline solution into the urinary bladder, at a constant rate of 0.1 ml/minute. The intraluminal-pressure signal during infusion of saline into the bladder is continuously recorded on a polygraph (Rectigraph-8K San-ei with BM614/2 amplifier from Biomedica Mangoni) .The cystometrogram is used to evaluate the urodynamic parameters of bladder volume capacity (BVC) and micturition pressure (MP). BVC (ml) is defined as the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. MP (mmHg) is defined as the maximal intravesical pressure caused by contraction during micturition. Basal BVC and MP values are evaluated as mean of the values observed in the cystometrograms recorded in an initial period of 30-60 minutes. Following determination of basal BVC and MP, the infusion is interrupted and the test compounds are administered orally by a stomach tube. Bladder infusion is resumed and changes in BVC and MP are evaluated from the mean values obtained in the cystometrograms observed during 1, 2, 3, 4 and 5 hours after treatment. Compounds are administered in a volume of 2 ml/kg and groups of control animals receive the same amount of vehicle (0.5% methocel in water) orally.

Statistical analysis

Data are expressed as mean ± standard error. The percent changes of BVC and MP *versus* the basal values, as well as Δ values (difference in ml or mmHg) of BVC and MP (BVC or MP at time "x" minus basal value), are evaluated for each rat/time. Data are reported as % changes *versus* basal values.

Statistical analysis on BVC and MP values, as well as on Δ values, is performed by S.A.S./STAT software, version 6.12. The observed differences between vehicle (control) and test treatments are evaluated on Δ values of BVC and MP, whereas the differences between the values at different times *versus* basal values are analyzed on

original BVC and MP data.

Example 9 Inhibition of stereotypy (rhythmic forepaw treading) induced by 8-OH-DPAT in rats (post-synaptic antagonism)

A. Method:

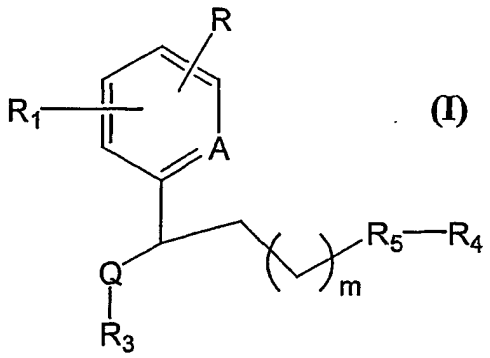
The inhibitory effect of 5-HT_{1A}-receptor antagonists on stereotyped forepaw treading induced in rats by subcutaneous injection of 8-OH-DPAT is evaluated by the method of Tricklebank (Tricklebank et al., *Eur. J. Pharmacol.*, 117: 15, 1985) with minor modifications as described below.

Male Sprague-Dawley rats [Crl: CD® (SD) IGS BR] weighing 150-175 g from Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature. On the day of the experiment, the rats are placed singly in clear plastic containers, 10-15 minutes before administration of the vehicle or compounds to be tested. For evaluation of antagonistic activity after oral administration, the compounds are administered 1 and 4 hours before induction of stereotypy by 8-OH-DPAT (1 mg/kg subcutaneously). Observation sessions last 30 seconds and begin 3 min after 8-OH-DPAT treatment and were repeated every 3 minutes over a period of 15 minutes.

The appearance of the symptom induced by postsynaptic stimulation of 5-HT_{1A} receptors is noted, and the intensity is scored using an intensity scale in which: 0 = absent, 1 = equivocal, 2 = present and 3 = intense. Behavioural scores for treated rats are accumulated throughout the observation time (5 observation periods) and expressed as mean values of 4 rats/dose. Change in mean values of treated animals in comparison with control (vehicle) group, expressed as per-cent inhibition, was used to quantify the antagonistic activity.

CLAIMS

1. A compound having the general formula I



(I)

wherein

R represents a hydrogen atom or one or more halogen atoms or (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_1-C_6)-haloalkyl, (C_1-C_6)-haloalkoxy, (C_1-C_6)-hydroxyalkyl, alkoxy-(C_1-C_6)-alkyl, nitro, amino, (C_1-C_6)-aminoalkyl, (C_1-C_6)-alkylamino, N-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl, N, N-di-(C_1-C_6)-alkylamino, acylamino, (C_1-C_6)-alkylsulphonylamino, aminosulphonyl, (C_1-C_6)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkylcarbonyl-(C_1-C_6)-alkyl, formyl, alkanoyloxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylaminocarbonylamino, (C_1-C_6)-alkylsulphinyl, (C_1-C_6)-alkylsulphonyl, and N, N-di-(C_1-C_6)-alkylaminosulphonyl groups;

R_1 represents a hydrogen atom or a cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclic, heterocycloxy, heterocycloalkyl or heterocycloalkoxy group, each group being optionally substituted with one or more substituent R as above defined;

Q represents a carbonyl or hydroxymethylene group or a group of the formula -CH(OR_2)- where R_2 represents a (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl or cycloalkyl group, each of which is optionally substituted with one or more groups selected from R_8 and R_9, where R_8 is selected from the group consisting of halo, (C_1-C_6)-alkoxy, (C_1-C_6)-haloalkoxy, cyano, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl groups and R_9 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R_2 represents -C(O)- (C_1-C_6)-alkyl, -C(O)O-(C_1-C_6)-

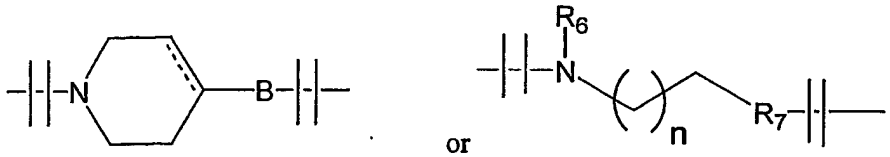
alkyl, -C(O)$NR_{10}R_{11}$ or -C(S)$NR_{10}R_{11}$ wherein each of R_{10} and R_{11} independently represents a hydrogen atom or a (C_1-C_6)-alkyl group;

R_3 represents a (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted with one or more substituent R or R_1, defined as above;

R_4 represents an aryl or heterocyclic group, each of which is optionally substituted with one or more substituents R, defined as above;

A represents CH or N,

R_5 represents



(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

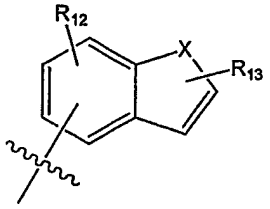
R_6 represents H or alkyl,

R_7 represents O, S, NR_6 or CH_2;

B represents a bond, O, S, NR_6 or CH_2; and

------- represents a single or double bond,

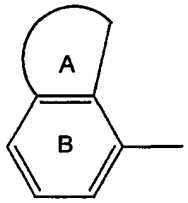
with a proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)- or -CH(OH)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, alkylthio, hydroxy, halo, haloalkyl, nitro, amino or cyano groups; R_1 represents a hydrogen atom or a phenyl or alkylphenyl group; R_3 represents a cycloalkyl, aryl or heterocycic group, each of which is optionally substituted with one or more substituent selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_1-C_6)-haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2; and R_4 represents the group



wherein X represents O, S, NH, N(C_1-C_6-alkyl), S(=O) or S(=O)$_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo,

hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, N-(C_1-C_6)-alkylamino, N, N-di-(C_1-C_6)-alkylamino, aminocarbonyl, N-(C_1-C_6)-alkylaminocarbonyl, N, N-di-(C_1-C_6)-alkylaminocarbonyl and acylamino groups, and

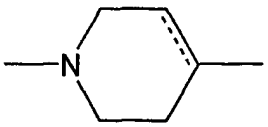
and further with the proviso that the substituents of formula I are not such that simultaneously Q represents-C(O)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl, and alkoxycarbonyl groups; R_1 represents hydrogen; R_5 represents group (i) wherein B represents a bond or CH_2; R_4 represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups; or R_4 represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R_3 represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups,

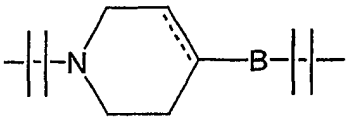
or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

2. A compound having the general formula I wherein R, R_1, R_3, R_4, R_5, Q, A and m are as defined in claim 1, provided that, if Q represents a carbonyl or hydroxymethyl group and R_5 represents a group of formula

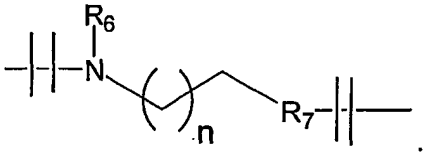


then R_3 is not a heterocyclic group attached to Q by a C-N bond and R_4 is not a substituted or unsubstituted 7-indolyl, 7-benzofuranyl or 7-benzothienyl group.

3. A compound according to claim 1 or claim 2 wherein R_5 represents



4. A compound according to claim 1 or claim 2 wherein R_5 represents



5. A compound according to any of claims 1 to 4 wherein R_3 represents a hydrogen atom or a $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl group, each group being optionally substituted with one or more substituent R or R_1 as defined in claim 1.

6. A compound according to claim 5 wherein R_3 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t.butyl, vinyl, allyl, prop-1-enyl, 1-methylvinyl, 2-methylallyl, ethynyl or prop-1-ynyl group.

7. A compound according to any of claims 1 to 4 wherein R_3 represents a cyclohexyl or 2-thienyl group.

8. A compound according to any of claims 1 to 7 wherein R_4 represents an unsubstituted heterocyclic group or a phenyl group substituted with one or more halogen atoms or $(C_1$-$C_6)$- alkyl, $(C_1$-$C_6)$-alkoxy or $(C_1$-$C_6)$-haloalkoxy groups.

9. A compound according to claim 8 wherein R_4 represents a 5-(2,3-dihydro-1,4-benzodioxinyl), 4-indolyl, 8-quinolyl, 2-methoxyphenyl, 2,6-dimethylphenyl, 4-fluoro-2-

methoxyphenyl or 2-(2,2,2-trifluoroethoxy)-phenyl group.

10. A compound according to claim 1, being

- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine or
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 10 or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt of such a compound in admixture with a pharmaceutically acceptable diluent, excipient or carrier.

12. A method of reducing the frequency of urinary bladder contractions in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

13. A method of treating neuromuscular dysfunction of the lower urinary tract in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

14. A method according to claim 13 whereby one or more of the conditions or symptoms of urinary urgency, overactive bladder, increased urinary frequency, incontinence, mixed incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the urinary bladder is ameliorated.

15. A method according to any of claims 12 to 14 wherein said mammal is a human.

16. A method according to any of claims 12 to 15 wherein the compound or composition is administered by an oral, enteral, intravenous, intramuscular, subcutaneous, transmucosal, transdermal or by-inhalation route.

17. A method according to any of claims 12 to 16 wherein the compound or composition is administered in combination with an antimuscarinic or α_1 antagonist.

18. A method according to claim 17 wherein said antimuscarinic is oxybutynin, tolterodine, darifenacin or temiverine.

19. A method according to claim 17 wherein said α_1 antagonist is prazosin, doxazosin, terazosin, alfuzosin or tamsulosin.

20. A method for treating disorders of the central nervous system caused by serotonergic dysfunction, the method comprising delivering an effective amount of a compound according to any one of claims 1 to 10 or of a composition according to claim 11 to the environment of a 5-HT_{1A} serotonergic receptor.

21. A method according to claim 20 wherein said compound or composition is delivered via an extracorporeal route.

22. A method according to claim 21 wherein said compound or composition is delivered by administering the compound to a mammal possessing the 5-HT_{1A} serotonergic receptor.

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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, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, 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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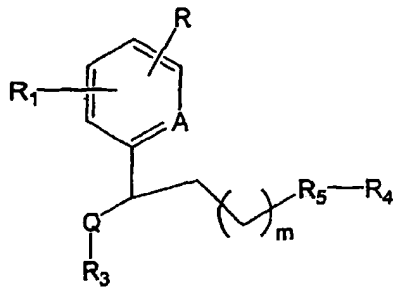
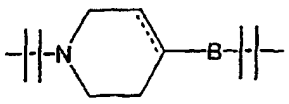
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

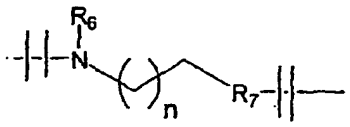
(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES WITH SEROTONINERGIC RECEPTOR AFFINITY



(I)



(II)



(III)

(57) Abstract: Compounds of formula (I), (A is CH or N, R and R_1 are a wide range of substituents, Q is CO, CHOH or $CHOR_2$, R_2 is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R_4 is an aryl or heteroaryl group, either of which is optionally substituted, R_5 is either (II) or (III), wherein m is 1 or 2, R_6 is H or alkyl, R_7 is O, S, NR_6 or CH_2, B is a bond, O, S, NR_6 or CH_2 and ------ represents a single or double bond) have affinity for serotoninergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.

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(88) Date of publication of the international search report:
17 June 2004

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.

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/EP 03/06290

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/14 C07D211/46 C07D215/26 A61K31/445 A61K31/451
A61K31/47 A61P13/00

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 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 671 440 A (DR. KARL THOMAE GMBH) 1965 Starting material 17 in the table on page 6 corresponding to formula III on page 5 ---	1,2,4-6
X	EP 0 680 962 A (ZENECA LTD) 8 November 1995 (1995-11-08) claims 1,3,6,9; examples 17,19,20,24,26,27,29 ---	1-3,11
X	US 5 585 374 A (CLIFFE IAN A ET AL) 17 December 1996 (1996-12-17) cited in the application claims; example 5 ---	1-22
X	WO 96 16961 A (AMERICAN HOME PROD) 6 June 1996 (1996-06-06) page 5, line 23 - line 32; claims; examples 2-5 --- -/--	1-22

[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
1 April 2004	23/04/2004

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	Hanisch, I

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Ir inal Application No
PCT/EP 03/06290

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 610 164 A (BAUDY REINHARDT B ET AL) 11 March 1997 (1997-03-11) column 3, line 11 - line 29; claims; example 2	1-22
X	EP 0 982 304 A (LILLY CO ELI) 1 March 2000 (2000-03-01) cited in the application claims 1-15,18-32; examples 1-52	1-22
X	US 5 610 295 A (CLIFFE IAN A ET AL) 11 March 1997 (1997-03-11) column 1, line 6 - line 13; claims 1-6,11,13	1-22
X	EP 0 924 205 A (LILLY CO ELI) 23 June 1999 (1999-06-23) paragraph '0010!; claims 1-16; examples 1-4,6-8	1-22

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 03/06290

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:

see FURTHER INFORMATION sheet PCT/ISA/210

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 12-22 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 03/06290

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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(54) Title: ASSAY

(57) Abstract: The invention relates to an assay to establish the affinity of compounds at the "ether-a-go-go" (ERG) potassium (K+) channel, in particular the human ERG (hERG) potassium channel, using a labelled inwardly rectifying potassium channel (IKR) blocker. This assay is useful to identify compounds with undesirable effects on cardiac repolarisation in man, in particular the propensity to prolong the QT interval in the electrocardiogram.

Assay

The invention relates to an assay to establish the affinity of compounds at the "ether-a-go-go" (ERG) potassium (K^+) channel, in particular the human ERG (hERG) potassium channel, using a labelled rapid delayed rectifying potassium channel (IKR) blocker, for example [^{3}H]-dofetilide or [^{3}H]-MK-499. This assay is useful to identify compounds with undesirable effects on cardiac repolarisation in man, in particular the propensity to prolong the QT interval in the electrocardiogram, which may lead to Torsades de Pointes.

In recent years the development of some compounds proposed for therapeutic use has been abandoned in late phase drug development due to the detection of undesirable effects on cardiac repolarisation in man. The effects of these drugs are assessed in terms of the QT interval in the electrocardiogram (ECG). The QT interval is the portion of an ECG that represents the time from the beginning of ventricular depolarization to the end of ventricular repolarisation. Because the QT interval can be affected by heart rate lengthening with a decrease in heart rate and shortening with an increase in heart rate, the QT is often "corrected" for heart rate, resulting in the QT_C interval. In rare cases the administration of some drug molecules results in a prolongation of the QT interval of the ECG in man. The ECGs of these patients resemble those of individuals suffering from an inherited disorder known as long QT syndrome. Drug-induced ventricular fibrillation, in these cases, can eventually lead to sudden death (Morganroth J et al. (1993) Am J Cardiol. 72, 26B-31B; De Ponti F. et al., (2000) Eur J. Clin. Pharmacol. 56, 1-18). A number of drug molecules, including, E-4031, cisapride and terfenadine, are all known to prolong the QT interval of the electrocardiogram in man (Fuliki A, *et al.* (1994), Cardiovascular Pharmacol. 23: 374-378; Van Haarst AD et al., (1998) Clin Pharmacol. Ther. 64: 542-546; Honig P.K. et al. (1993) J.A.M.A. 269; 1513-1518).

The launch of new drugs with undetected potentially cardiotoxic side effects could have hazardous consequences and could trigger lethal cardiac dysrhythmias in patients. Late detection of QT prolongation, induced by compounds of pharmacological interest can impede drug discovery and development programs, and consequently have a

profound impact on the outcome of a program. It is desirable, therefore, to test for the potential cardiotoxic side effects of compounds at an early stage of drug development.

According to the invention there is provided an assay that comprises, or consists of, the following steps:

a) incubation of cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG with labelled IKR blocker in assay buffer in the presence or absence of different amounts of a test compound or a mixture of test compounds;

b) determination of specifically bound labelled IKR blocker;

c) calculation of the inhibition of labelled IKR blocker binding by the test compound or mixture of test compounds.

The assay is useful as a preclinical predictive indicator for identification of compounds with a propensity to prolong the QT interval in man. The assay is a competitive binding assay that measures the ability of a test compound or mixture of compounds to displace labelled IKR blocker from the ERG K^+ channel (ether-a-go-go K^+ channel, herein called ERG). The assay can be performed in a high throughput test system. In conjunction with structure-activity relationships (SAR), ligand binding assays using labelled IKR blockers can be used to assist in the design of new drugs devoid of, or with reduced affinity to ERG, in particular human ERG (hERG).

The assay buffer used is particularly important for optimising binding of the IKR blocker or test compound(s) to ERG. It has been found that optimal assay performance is achieved using a Tris based buffer (pH 7.2 to 7.6, preferably pH 7.4 at room temperature) containing potassium (K^+) ions. Potassium ions in the assay buffer may be provided, for example as potassium choride (KCl). The concentration of potassium ions in the assay buffer determines the predictive value of the assay. Assays performed in assay buffer containing from 7.5 to 12.5mM KCl, preferably from 8.5 to 11.5mM KCl, most preferably 10mM KCl are particularly useful to provide an IC_{20} value predictive of onset of QT prolongation.

The assay buffer of the invention preferably comprises or consists of Tris.Cl and KCl. Optionally, $MgCl_2$ may be included in the assay buffer.

The concentration of Tris.Cl in the assay buffer is preferably from 30mM to 100mM Tris.Cl, more preferably from 30mM to 70mM Tris.Cl, yet more preferably from 40mM to 60mM Tris.Cl, further preferably from 45mM to 55 mM Tris.Cl, most preferably 50mM Tris.Cl.

The concentration of KCl in the assay buffer is preferably from 5 to 20mM KCl, more preferably from 6 to 15mM KCl, yet more preferably from 7.5 to 12.5mM KCl, further preferably from 8.5 to 11.5mM KCl, most preferably 10mM KCl.

In a particularly preferred embodiment, the assay buffer comprises or consists of from 30 to 100mM Tris.Cl and from 5 to 20mM KCl, preferably from 30 to 70mM or from 30 to 100mM Tris.Cl and from 6 to 15mM KCl, yet more preferably from 40 to 60mM Tris.Cl and from 7.5 to 12.5mM KCl, further preferably from 45 to 55mM Tris.Cl and from 8.5 to 11.5mM KCl.

It is particularly preferred that the assay buffer comprise or consist of 50mM Tris.Cl and 10mM KCl.

If $MgCl_2$ is included in the assay buffer, the concentration of $MgCl_2$ is preferably from 0.6mM to 2.0mM $MgCl_2$, more preferably from 0.6mM to 1.6mM $MgCl_2$, yet more preferably from 0.8mM to 1.4mM $MgCl_2$, further preferably from 0.9mM to 1.3mM $MgCl_2$, yet further preferably from 1.0mM to 1.2mM $MgCl_2$, most preferably 1.0mM or 1.2mM $MgCl_2$.

In a preferred embodiment the assay buffer used comprises or consists of from 30 to 100mM Tris.Cl, from 5 to 20mM KCl, and from 0.6 to 2.0mM $MgCl_2$, preferably from 30 to 100mM Tris.Cl or from 30 to 70mM Tris.Cl, from 6 to 15mM KCl, and from 0.6 to 1.6mM $MgCl_2$, yet more preferably from 40 to 60mM Tris.Cl, from 7.5 to 12.5mM KCl and from 0.8 to 1.4mM $MgCl_2$, further preferably from 45 to 55mM Tris.Cl, from 8.5 to 11.5mM KCl and from 0.9 to 1.3mM $MgCl_2$ or from 1.0 to 1.2mM $MgCl_2$.

The assay buffer may comprise or consist of 50mM Tris.Cl, 10mM KCl and 1.0mM $MgCl_2$; or 50mM Tris.Cl, 10mM KCl and 1.2mM $MgCl_2$.

It is preferred that the assay buffer be at a pH between 7.2 and 7.6 at room temperature; it is particularly preferred that the assay buffer be at pH 7.4 at room temperature.

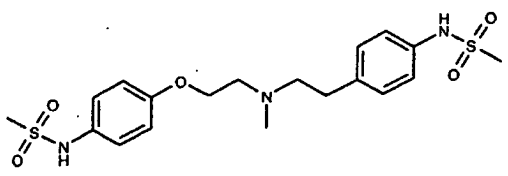
The ERG gene (cDNA) can be from a vertebrate or invertebrate source; for vertebrates the ERG gene may be from a mammalian source (e.g. human, simian, bovine, porcine, canine, rabbit, guinea pig, rat, or mouse) or an invertebrate source such as an insect source (e.g. drosophila). A prokaryotic homologue of mammalian ERG may be used. It is preferred that the ERG gene be mammalian ERG, in particular human ERG (hERG) or canine ERG (cERG).

The ERG gene may be expressed in a mammalian cell line e.g. HEK-293 (Human embryonic kidney) cells, CHO (Chinese hamster ovary) cells; CHL (Chinese hamster lung) cells, COS (monkey) cells; or in an insect cell line e.g. SF9. A baculovirus vector system can be used for expression of ERG in a compatible insect cell line. Alternatively, ERG may be expressed in yeast or bacterial cells. It is preferred that the ERG gene is hERG or cERG and is expressed in either HEK-293, CHO or CHL cells.

The assay may be performed using whole cells expressing ERG or membrane preparations derived from cells expressing ERG, or membrane preparations derived from tissue expressing ERG.

Dofetilide is an IKR blocker (selective inhibitor of the rapid component of the delayed rectifier potassium current), which prolongs the action potential duration and the effective refractory period in a concentration-dependent manner. Clinical studies have demonstrated that dofetilide is effective in treating patients with atrial as well as ventricular arrhythmias. Dofetilide has formula I below.

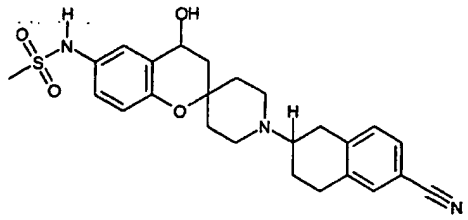
Formula I



Dofetilide is claimed and its preparation is described in European patent EP 0245997.

MK-499 (Merck) is methylsulphonamide antiarrhythmic drug that acts as an IKR blocker. MK-499 has formula II shown below.

Formula II



The IKR blocker used in the assay is labelled with a detectable label, for example a radiolabel or fluorescent tag. In a preferred embodiment of the invention, the labelled IKR blocker used in the assay is labelled dofetilide, preferably radiolabelled dofetilide, most preferably tritiated dofetilide ([^{3}H]-dofetilide). In another embodiment of the invention, the labelled IKR blocker used in the assay is labelled MK-499, preferably radiolabelled MK-499, most preferably tritiated MK-499 ([^{3}H]-MK-499).

Preferred assay formats include the filter binding technique, whereby bound and unbound labelled IKR blocker e.g. labelled dofetilide or labelled MK-499; preferably radiolabelled dofetilide or radiolabelled MK-499; most preferably [^{3}H]-dofetilide or [^{3}H]-MK-499, are separated by filtration. The assay can be performed utilising the scintillation proximity assay (SPA) technique, using radiolabelled IKR blocker e.g. radiolabelled dofetilide or radiolabelled MK-499, preferably [^{3}H]-dofetilide or [^{3}H]-MK-499.

In the filter binding technique, cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG are incubated in assay buffer with labelled IKR blocker e.g. [^{3}H]-dofetilide or [^{3}H]-MK-499, in the presence (test) or absence (control) of the test compound or mixture of test compounds. Incubations are preferably carried out at room temperature for from 60 to 120 minutes, preferably for 90 minutes. Non-specific binding is determined in the

presence of unlabelled IKR blocker, e.g. 10μM dofetilide or 10μM MK-499. Bound labelled IKR blocker is separated from unbound IKR blocker by filtration through filter mats, or onto multiwell filter plates. Filter mats or plates are washed to remove unbound labelled IKR blocker, bound labelled IKR blocker is quantified e.g. for tritiated IKR blocker such as [^{3}H]-dofetilide or [^{3}H]-MK-499 by scintillation spectroscopy using an appropriate counter for radioactivity.

In the scintillation proximity assay™ (SPA) system (Amersham Biosciences), beads are used to bind cells expressing ERG or membranes derived from cells expressing ERG or membranes derived from tissue expressing ERG. A variety of bead types are suitable for use in a SPA assay according to the invention, these include PVT wheat germ agglutinin, yttrium oxide polylysine beads, or yttrium silicate beads (YSi) (Amersham Biosciences) such as YSi polylysine or YSi wheat germ agglutinin. The optimum bead type for use in a SPA assay of the invention depends on the cells or cell membranes used; bead to cell or bead to membrane binding may be assessed to identify the optimum bead type for the cell or cell membrane used. Beads bound to ERG material (whole cell, cell membrane preparation or tissue membrane preparation) are incubated in assay buffer with labelled IKR blocker, e.g. [^{3}H]-dofetilide or [^{3}H]-MK-499 in the presence (test) or absence (control) of the test compound or mixture of test compounds. The ability of the test compound or mixture of test compounds to displace bound radiolabelled IKR blocker is determined by detecting light emissions, for example using standard counters that can be used with SPA technology.

The assay may also include one or more of the steps of: calculation of the concentration of the test compound(s) that gives 20% inhibition of dofetilide binding (IC_{20}), calculation of the concentration of the test compound(s) that gives 50% inhibition of dofetilide binding (IC_{50}), calculation of the compound affinity as Ki or calculation of the compound affinity as pKi.

The IC_{20} values generated from competitive displacement of IKR blocker binding, e.g. [^{3}H]-dofetilide binding, using the assay of the invention are comparable to the free drug concentration associated with QT prolongation in man. Thus the assay can be used to predict the concentration of a compound liable to cause undesirable cardiac side effects.

To assess whether a compound, or mixture of compounds, is likely to prolong the QT interval in the electrocardiogram in man, the following steps are carried out:

a) An assay is carried out according to the invention.

b) An IC_{20} value is obtained; this indicates the real or predicted free drug concentration at which QT prolongation will occur in man;

c) The IC_{20} value is compared with the free drug concentration required for the desired therapeutic effect of the compound or mixture of compounds in vivo.

If the free drug concentration required for the desired therapeutic effect of the compound or mixture of compounds is within 10 to 30 fold of the IC_{20} of the compound or mixture of compounds in the assay, the compound or mixture of compounds is likely to show QT interval prolongation in man.

The assay of the invention is a better predictor of *in vivo* QT prolongation effect of drug molecules than existing assays such as the HERG patch clamp assay.

List of Figures

Figure 1: Representative saturation curve data for [^{3}H]-dofetilide binding to HERG in (a) filter binding, (b) SPA 96 well format and (c) SPA 384 well format.

Figure 2: Correlation plots comparing p*K*i values obtained from filter binding and SPA binding assays: (a) correlation between 96 well hERG [^{3}H] dofetilide SPA assay and radioligand binding assay, (b) correlation between 96 well and 384 well hERG [^{3}H] dofetilide SPA assay.

Figure 3: Comparison of inhibition of [^{3}H]-dofetilide binding to hERG, hERG patch clamp, and free drug concentration known to induce QT interval prolongation in man, for (a) E-4031, (b) dofetilide, (c) terfenadine and (d) cisapride.

Figure 4: Comparison of the dofetilide IC_{50} in the dofetilide binding assay carried out in cell membranes from HEK-293 cells transfected with human ERG (hERG (▲)) or with canine ERG (cERG (■))

Figure 5: Comparison of terfenadine IC_{50} in the dofetilide binding assay in cERG or hERG transfected HEK-293 cell membranes

Figure 6: Comparison of E4031 IC_{50} in the dofetilide binding assay in cERG or hERG transfected cell HEK-293 membranes

Figure 7: Mean (n = 2) concentration effect curves for (a) dofetilide and (b) terodiline in tritiated dofetilide SPA assays using assay buffer 50mM Tris Cl, 10mM KCl, at pH7.4.

Examples

Example 1: Preparation of membranes from HEK-293 cells expressing human or canine ERG

An adherent HEK-293 cell line expressing human ERG (Zhou, Z et al (1998) Biophys. J. 74, 230-241) was provided by Dr. Craig January, University of Wisconsin, USA; this cell line was designated the "January" cell line. An alternative adherent HEK-293 cell line, designated cell line 15 (293S-HERG clone 15) was produced by the method described in Zhou, Z et al (1998). Full length cDNA for human ERG was inserted downstream of the CMV promoter in pcDNA3.1 (Invitrogen), the vector also has a SV40 promoter that drives expression of a neomycin resistance gene. The construct was transfected into human embryonic kidney 293S (HEK-293) cells. Stable transformants were selected using G418 (Gibco). Although cell line 15 has slightly lower expression of hERG than the January cell line, it has improved growth characteristics.

Cell line 15 (293S-HERG (Clone 15)) was deposited on 26 June 2002 with the ECACC (CAMR Salisbury, Wiltshire, SP4 OJG, UK) in accordance with the terms of the Budapest Treaty 1977 under deposit accession number 02062678.

Adherent HEK-293 cells expressing human ERG, were grown in MEM Earles medium (Life Technologies) supplemented with 10% foetal calf serum (PAA Laboratories), 2 mM L-glutamine (Sigma), 1 mM sodium pyruvate (Sigma), 0.4 mg/ml G418 (Life Technologies) and an addition of 1x non-essential amino acids (Life Technologies). The cells were grown at 37°C in a humidified atmosphere with 5% CO_2 in T225 cm^3 flasks.

The cells were split 1:3 to 1:5 after reaching 80% confluence using cell dissociation solution (Sigma, cat no: C5914 in 2001) and later seeded into 850 cm^2 CO_2 gassed roller bottles (Corning, cat no: 430849 in 2001) in the absence of G418.

For the preparation of membranes, cells were harvested from the roller bottles by scraping and resuspended in PBS (Life Technologies, cat no: 14190-094 in 2001). All cells were pelleted, washed twice with PBS and snap-frozen on dry ice prior to storage at –80°C until required.

A HEK-293 cell line expressing canine ERG was produced by transient transfection of HEK-293 cells. The complete coding sequence of cERG cDNA (Zehelein et al (2001). Pflugers Archiv. European Journal of Physiology. 442(2): 188 – 191) was provided in the pBluescript® vector (Stratagene) by Professor Zehelein University of Heidelberg, Germany. In the pBluescript construct, the cERG cDNA was flanked by *Bam*HI Sites. Initial experiments indicated poor insertion efficiency for direct insertion of cERG *Bam*HI fragment into the desired vector, pcDNA3.1. To overcome this, an indirect cloning method was devised using the cloning vector pSP73 (Promega). The cERG/pBluescript construct and pSP73 vector were subjected to *Bam*HI digestion, to reduce interference by the presence of pBluescript *Bam*HI fragments in the ligation reaction, the cERG/pBluescript *Bam*HI digested material was also subjected to *Sca*I digestion to cleave pBluescript and ensure more effective separation of the cERG *Bam*HI fragment on agarose gel. The restriction mixtures were subjected to agarose gel electrophoresis, bands containing the cERG and pSP73 *Bam*HI fragments were visualized following staining with ethidium bromide and UV illumination. The cERG and pSP73 bands were excised and eluted from the gel using a QIAgen MinELute Gel extraction kit according to the manufacturers instructions. To prevent religation of the *Bam*HI ends of the pSP73 DNA during the ligation reaction, the plasmid DNA fragments were subjected to CIP treatment using a standard protocol. The cERG *Bam*HI fragments were ligated into the pSP73 *Bam*HI fragments using a standard ligation protocol. After the reaction, the ligation mixture was transformed into cJM109 competent *E. coli* cells using a standard transformation protocol. Transformants were selected by plating on LB agar (Millers) containing ampicillin (50µg/ml) and incubated overnight at 37°C. Overnight cultures of the transformed cells were used to produce mini preparations of cERG/pSP73 DNA using a QIAgen Miniprep kit according to the

manufacturer's instructions. The resulting DNA was subjected to restriction digestion and agarose gel electrophoresis to identify positive clones.

The cERG cDNA was excised from cERG/pSP73 as an *Xho*I (5') *Eco*RI (3') fragment, this fragment was ligated into an *Xho*I/*Eco*RI fragment of the reverse poly linker form of pcDNA3.1, pcDNA3.1(-) *Xho*I/*Eco*RI. In this instance the reverse polylinker form was used because the cERG/pSP73 clone selected contained the reverse orientation of cERG. After ligation into pcDNA3.1(-), the 5' end of cERG was located adjacent to the enhancer-promoter sequence from human cytomegalovirus (CMV). The ligation mixture was transformed into cJM109 competent *E. coli* cells using a standard transformation protocol, transformants were selected via plating onto LB agar (Millers) containing ampicillin (50µg/ml) and incubating overnight at 37°C along with required controls. Colonies picked at random from the cERG/pcDNA3.1(-) plates were inoculated into 5ml of LB media containing ampicillin (50µg/ml) and incubated at 37°C, 200rpm overnight. These overnight cultures were subsequently used to produce mini-preps of DNA using a QIAgen Miniprep Kit. The resulting DNA was subjected to a *Xho*I and *Eco*RI double digestion and analysis on 1% agarose gel. No positive cERG/pcDNA3.1(-) clones were identified because of low insertion efficiency in the ligation reaction coupled with the fact that DNA from only a small number of clones was analysed using the mini prep method. A colony PCR method was thus used to screen a larger number of colonies for positive clones.

The colony PCR protocol permitted rapid detection of cERG/pcDNA3.1(-) clones. Three primers were designed and made for use in the PCR protocol:

Primer 1: 'CERG01' (SEQ ID NO: 1) which hybridises to cERG at nucleotide positions 601-620 of the coding sequence:

5'-ACCACATCCACCAGGCACAG-3'

Primer 2: 'NHE PCDNA3' (SEQ ID NO: 2) which hybridises to pcDNA3.1(-) at nucleotide positions 886-910 (within the multicloning site flanking the *Nhe*1 cloning site):

5'-CCCAAGCTGGCTAGCGTTTAAACGG-3'

Primer 3: 'T7 SP73' (SEQ ID NO: 3) which was used as a control and used against a colony known to produce cERG/pSP73. This hybridised to pSP73 at nucleotide positions 98-121, within the T7 polymerase promoter sequence:

5'-TAATACGACTCACTATAGGGAGA-3'

Ninety-five cJM109 colonies were picked from the LB agar transformation plates and transferred to a sterile deep well 96-well plate containing 1ml/well LB broth supplemented with ampicillin (50µg/ml). As a control, a colony known to contain the cERG/pSP73 plasmid was transferred to the final 96th well containing LB-amp broth. The plate was covered and incubated at 37°C overnight at 200rpm. An aliquot of 70µl of each mini-culture was transferred to a 96-well PCR plate (0.5ml/well) and placed in a Beckman Allegra 6R centrifuge for 2800rpm, room temperature for 10 minutes. The supernatant was discarded and the plate drained for 3 minutes. The PCR reaction mixes were set up and added to the PCR plate containing the bacterial pellets as follows:

	Test wells	Control well cERG/pSP73
Taqman Gold buffer (X10)	10.0µl	10µl
dNTPs (X10, 2mM/dNTP)	2.0µl	2µl
Taqman Gold Polymerase (5u/µl)	0.5µl	0.5µl
CERG01 (primer 1- 25µM)	2µl	2µl
NHE PCDNA3 (primer 2- 25µM)	2µl	-
T7 SP73 (primer 3- 25µM)	-	2µl
Nuclease free water	83.5µl	83.5µl

The bacterial pellet was resuspended in the PCR reaction mixture. The PCR reaction was performed as specified by the manufacturers protocol for the Taqman Gold PCR kit (Applied Biosystems, 1999 edition) thus:

	Temperature	Time	
Step 1 - hot start	95°C	6 minutes	
Step 2 - denaturation	95°C	1 minute	
Step 3 - annealing	60°C	1 minute	
Step 4 - extension	72°C	1 minute	*To step 2 for 35 cycles, then step 5.*

Step 5 - denaturation	95°C	45 secs
Step 6 - annealing	60°C	45 secs
Step 7 - extension	72°C	5 minutes

The PCR products for each well were then separated by electrophoresis on a 1.5% agarose gel using a 100bp DNA ladder marker at 100V for 25 minutes in 1X TAE buffer and visualised using UV light. Putative positive clones were identified and samples from these PCR reaction mixtures were run on a second separate 1.5% agarose gel at 100V for one hour to examine the sizes of the PCR products.

The mini-cultures which gave an amplified a PCR product were each seeded from the original deep-well 96-well plate into sterile tubes with 5ml LB broth containing 50µg/ml ampicillin and incubated at 37°C overnight at 200rpm. The overnight cultures were then used to produce mini-preps of DNA using a QIAgen Miniprep Kit. The resulting DNA was subjected to an *Xho*I and *Eco*RI double digestion to check for the presence of cERG/pcDNA3.1(-). The restriction digest was analysed via a 1% agarose gel run for 1 hour at 100V with 1kb DNA ladder markers (20µl sample loading with 2µl gel loading solution). Further restriction digestion analysis was performed to confirm that the purified plasmids from the transformants were indeed cERG/pcDNA3.1(-).

Untransfected HEK-293 cells were routinely maintained in 50ml Minimum Essential Medium (MEM) supplemented with 10% (v/v) foetal calf serum (FCS), 2mM L-glutamine, 1mM sodium pyruvate and 1mM non-essential amino acids. Cells were seeded into 225cm^2 ventilated cap flasks and were maintained in a humidified atmosphere containing 5% CO_2. The HEK-293 cells used in this study were between passage numbers 39-48. Cells were passaged typically every three days in a ratio of 1:3 from a flask of 80-90% confluency; fresh medium was added after washing twice with 10ml PBS and dissociating from the flask using cell dissociation fluid.

The cERG/pcDNA3.1(-) construct was transfected into HEK-293 cells grown to 80-95% confluency in 225cm^2 ventilated flasks using the following method. Endotoxin free cERG/pcDNA3.1(-) DNA (94µg) and Lipofectamine2000 (Gibco BRL) (94µg) were added to 2.25ml of OPTIMEM-I media (Gibco BRL) in sterile 10ml centrifuge tubes; mixing was carried out after incubation at room temperature for five minutes. The

Lipofectamine2000/DNA/OPTIMEM-I mix was then incubated at room temperature for twenty minutes before the addition of a further 10.5ml OPTIMEM-I. HEK-293 cells were washed with 10ml PBS and the Lipofectamine2000/DNA/OPTIMEM-I mixture added and incubated for 3.5 hours at 37°C in a humidified atmosphere containing 5% CO_2. After incubation, 50ml of MEM (supplemented with 10% (v/v) FCS, 2mM L-glutamine, 1mM sodium pyruvate and 1mM non-essential amino acids) was added. The HEK-293 cells were incubated for 24 hours at 37°C. Transfected cells were harvested after 24 hours by washing with PBS, scraping the cells into 10ml PBS and centrifuging at 1000rpm for 5 minutes at room temperature. The resulting cERG/pcDNA3.1(-) transfected HEK-293 cell pellet was stored at -80°C until required.

Preparation of membranes from HEK-293 cells expressing human or canine ERG

Cell membrane fractions were prepared from frozen aliquots of cells. All procedures were carried out at 4°C unless otherwise stated. Frozen aliquots of cells were thawed at room temperature and resuspended in assay buffer (e.g. 50mM Tris.Cl, 10mM KCl, 1 to 1.2mM $MgCl_2$, pH7.4, or 50mM Tris.Cl, 10mM KCl, pH7.4). The cells were then disrupted by homogenisation in an Omni LabTek homogeniser at 20,000 rpm for 30 seconds. The homogenate was centrifuged for 20 minutes at 48,000xg (4°C, Sorvall RC5B centrifuge) and the supernatant removed. The resulting pellets were resuspended in assay buffer and homogenised as above for 10 seconds. The pellets were collected by centrifugation and the final pellet resuspended in assay buffer. Protein content was determined using a Coomassie Blue based protein assay kit. Aliquots were stored at -80°C until needed; when stored in these conditions, the binding ability of the cell membrane fractions proved to be stable for at least 4 months.

Example 2: Filter binding assay with [^{3}H]-dofetilide

[^{3}H]-dofetilide (80-83 Ci/mmol) was synthesized by catalytic tritiation (a custom service provided, for example, by Amersham Life Science). However, other detectable labels known to the skilled person can be used instead of ^{3}H, e.g. fluorescent tags, other radiolabels, antibodies etc.

On the day of the assay, test compounds were dissolved at 1 mM in 50% DMSO or 100% DMSO, and then diluted to the desired concentrations (e.g. up to 100μM, or up to

the boundaries of solubility for the compound) in assay buffer. The final DMSO concentration in assay incubations is preferably 1.0 to 1.5% or less for optimal assay conditions.

Incubations included membrane homogenate at 50µg/ml in assay buffer (50 mM Tris.Cl, 10mM KCl, 1.0mM to 1.2mM $MgCl_2$, pH7.4) unless otherwise indicated, [^{3}H]-dofetilide (4 to 7nM) and test compound or mixture of test compounds or control vehicle. Filtration assays were incubated at room temperature for 90 minutes. Non-specific binding was determined in the presence of 10 µM dofetilide and was usually less than 15 % of total binding. Bound ligand was separated from free ligand by rapid filtration through GF/B glass fibre filter mats using, for example, a Brandel cell harvester, or onto GF/B Unifilter 96-well filter plates (Packard) using a Packard Filtermate 96 harvester. Filter mats and plates were pre-soaked in 5% PEI (w/v) for 60 minutes and washed after harvesting with 3 x 1 ml washes of ice-cold assay buffer. Unifilter plates were air dried for a minimum of 1.5 hours at 37°C prior to the addition of Microscint-0 (Packard). Bound [^{3}H]-dofetilide was determined by liquid scintillation spectroscopy using an appropriate counter, for example in a Packard TopCount Scintillation Counter (NXT Counter) or Wallac Counter (Trilux) for Unifilter plates and in a Wallac Big Spot Counter when filter mats were used.

In each experiment, triplicate assays were routinely performed and the data were averaged. Specific binding was analysed by nonlinear regression fit using GraphPad Prism software (GraphPad, San Diego). IC_{50} values were derived from a 4 parameter logistic fit using PRISM and converted to K*i* values by use of the Cheng & Prusoff equation; IC_{20} values were extrapolated from the graph.

Example 3: Scintillation proximity assay

The scintillation proximity assay (SPA) was carried out in assay buffer consisting of 50mM Tris.Cl, 10mM KCl, 1.0mM to 1.2mM $MgCl_2$, pH7.4, or using assay buffer consisting of 50mM Tris base, 10mM KCl, pH7.4. Bead to membrane binding was assessed to determine the optimum bead type for the cell line used. YSi wheatgerm agglutinin beads were used with cell membranes derived from the January HEK-293 hERG expressing cell line; YSi polylysine beads were used in studies using membranes

derived from Cell Line 15 (HEK-293 hERG expressing cell line). Conditions were optimised with respect to bead and cell membrane homogenate concentration, prior to characterising ERG pharmacology. The incubations (200 µl total per well for 96 well plates and 60 µl total per well for 384 well plates) included 25 µg of cell membrane homogenate per mg of bead. The membrane homogenate was precoupled with the YSi Wheatgerm Agglutinin or YSi polylysine bead suspension at 4°C on a roller shaker for approximately 2 hours. For competition binding assays, membrane homogenate bead suspension was incubated in white clear bottom 96 or 384 well plates with 5nM [^{3}H]-dofetilide in the absence and presence of competitor i.e. the test compound or mixture of test compounds. The plates were incubated at room temperature and shaken for approximately 1 hour. Beads were allowed to settle for a minimum of 30 minutes before plates were counted for retained radioactivity on a TopCount NXT scintillation counter. Nonspecific binding i.e. background count, was determined by the addition of 10µM dofetilide. Background counts were usually less than 15% of the total binding. For saturation studies, specific binding of [^{3}H]-dofetilide was determined over a range of concentrations (5 to 500nM) in the absence or presence of cold (i.e. unlabelled) 10µM dofetilide.

Example 4: Assay optimisation

a) Effect of Hepes- and Tris-based buffers on dofetilide binding

To optimise the specific binding of dofetilide to homogenates of cell membranes containing ERG, the interaction of [^{3}H]-dofetilide with the cell membrane preparation was examined in the presence of Hepes-based buffer (25mM Hepes, 135mM NaCl, 5mM KCl, 1mM $MgSO_4$, 50mM $CaCl_2$, pH7.4) and Tris-based buffer (50mM Tris.Cl, 10mM KCl, 1mM or 1.2mM $MgCl_2$). Comparison of the specific binding in these buffers revealed that percentage specific binding was similar in both Tris-based and Hepes-based buffers. However, as shown in Table 1, specific counts were twice as high in the presence of Tris-based buffer compared to those detected in Hepes-based buffer.

Table 1. Comparative effects of Tris-based and Hepes-based buffers on [^{3}H]-dofetilide binding to cell membrane homogenate expressing hERG.

Buffer	25mM HEPES free acid 135mM NaCl, 5mM KCl 1mM $MgSO_4$, 50 µM $CaCl_2$ pH 7.4 at room temp	50mM Tris 10mM KCl and 1.0 or 1.2mM $MgCl_2$ pH 7.4 at room temp
Total Binding (ccpm)	8510 ± 669	19627 ± 1189
Non-specific Binding (ccpm)	321 ± 27	315 ± 23
Specific Binding (ccpm)	8189	19312
% Specific Binding	96	98

Total and non-specific binding data represent arithmetic mean ± standard error mean of 14 individual wells per buffer split over two assays, performed at a protein concentration of 75µg/ml and a mean [^{3}H]-dofetilide concentration of 6.7nM. Incubation was carried out for 60 minutes at room temperature. ccpm=corrected counts per minute.

So that the maximum specific binding window could be achieved, the assay buffer used in Examples 1 to 8 was the Tris-based incubation buffer (50mM Tris.Cl, 10mM KCl, 1mM $MgCl_2$). Additionally, experiments were performed to optimise the cell membrane protein concentration and bead concentration for filter and SPA binding assays.

b) Saturation binding

Time courses were performed to determine optimal incubation time for binding activities. Incubation times were similar for both filter binding and SPA assays. The filter binding assay reached equilibrium in 90 minutes, SPA required 60 minutes. [^{3}H]-dofetilide binding to ERG in both filter binding and scintillation proximity assays was saturable with a K_D of 5.08 ± 1.0nM for filter binding and K_D values of 8.9 ±0.6nM and 9.1 ±1.8nM for 96 and 384 format scintillation proximity assays respectively (Figure 1a-c, with Fig. 1a showing the results of the filter binding assay, Fig. 1b the results of the SPA in 96-well format, and Fig. 1c showing the results of the SPA in 384 well format). Non-linear curve fitting of this data indicated that binding was to a single site. A B_{max} of 7.4 ± 0.7pmol/mg protein for [^{3}H]-dofetilide was obtained from filter binding (Figure 1). As scintillation proximity assays do not give an accurate determination of dpm (disintegrations per minute) values, a B_{max} is not quoted for SPA.

c) Comparison of SPA and filter binding techniques

A comparison of SPA and filter binding techniques revealed excellent concordance of results. Affinity values displayed excellent correlation between the two assay types and the rank order of compound affinity is identical, as is shown in Figure 2 (correlation plots comparing p*K*i values obtained from filter binding and SPA binding assays).

d) Competitive binding studies

A range of compounds, including hERG blockers known to prolong the QT interval in man, was examined for competitive displacement of [^{3}H]-dofetilide. E4031, dofetilide, terfenadine, and cisapride produced complete inhibition of specific binding with a range of calculated affinity values that are summarised in Table 2.

Table 2. Affinity values for compounds tested against [^{3}H]-dofetilide filter and SPA binding assays to HERG.

Compound	Filter binding	SPA 96	SPA 384
	p*K*i	p*K*i	p*K*i
Dofetilide	8.22 ± 0.04	8.05 ± 0.54	8.26 ± 0.12
E4031	7.82 ± 0.03	7.81 ± 0.05	7.89 ± 0.11
Terfenadine	7.53 ± 0.09	7.75 ± 0.07	7.72 ± 0.41
Cisapride	7.34 ± 0.05	7.15 ± 0.04	7.55 ± 0.22
Glibenclamide	< 5	< 5	< 5
D-Sotalol	< 5	< 5	< 5

Data expressed as p*K*i values (the negative logarithm of molar concentration of competing ligand to displace 50% of 5nM [^{3}H]-dofetilide binding). Data are the mean of at least n = 3 experiments.

Example 5: Prediction of QT interval prolongation effect of compounds in man

The IC_{20} values generated from competitive displacement of [^{3}H]-dofetilide binding using the assay of the invention are comparable to the free drug concentration associated with QT prolongation in man as is shown in Figure 3 for a range of compounds, including E-4031 (Figure 3a), dofetilide (Figure 3b), terfenadine (Figure 3c) and cisapride (Figure 3d). For each compound, the inhibition of dofetilide binding in the binding assay (filter binding technique), and in a hERG patch clamp assay is compared with the concentration of free drug associated with QT interval prolongation in man (Fuliki A, *et al.* (1994) Cardiovascular Pharmacol, 23: 374-378; Van Haarst AD et al. (1998) Clin Pharmacol. Ther. 64: 542-546; Honig PK, et al. (1993) J.A.M.A. 269: 1513-1518).

The ERG patch clamp assay provides a measure of the current through the ERG channel and indicates the number of ion channels present in a cell. However, due to the phenomena of state dependent block observed in patch clamp studies (Walker, B.D. et al (1999) British J. Pharmacol 128, 444-450) exhibited by a number of known hERG blockers with the propensity to prolong the QT interval *in vivo*, the ligand binding assay provides a better predictor of *in vivo* QT prolongation effect of a drug than the hERG patch clamp technique (Figure 3d).

To assess whether a compound or mixture of compounds is likely to prolong the QT interval in the electrocardiogram in man, the following steps are carried out:

a) A binding assay is carried out according to the invention, for example as as described in Example 2 or Example 3, to test the affinity of the compound or mixture of compounds for ERG, preferably hERG or cERG;

b) The IC_{20} is obtained, e.g. as described at the end of Example 2; the IC_{20} being the real or predicted free drug concentration at which QT prolongation occurs in man;

c) The IC_{20} value is compared with the free drug concentration required for the desired therapeutic effect of the compound in vivo.

If the free drug concentration required for the desired therapeutic effect of the compound is within 10 to 30 fold of the IC_{20} of the compound in the assay of the invention, the compound is highly likely to cause QT interval prolongation in man.

Example 6: Comparison of dofetilide binding assay carried out HEK-293 cells transfected with cERG or hERG.

The dofetilide binding assay was carried out as described Example 2 using HEK 293 cells transfected with either human ERG or canine ERG. The results are shown in figure 4, from which it can be seen that the IC_{50} for dofetilide is similar for canine and human ERG, being 13.9nM and 15.6nM respectively. IC_{20} values for dofetilide were 1.92nM and 2.15nM for canine and human ERG, respectively.

Example 7: Comparison of terfenadine competition assay using HEK-293 cells transfected with cERG or hERG

The dofetilide binding assay was carried out using terfenadine as the test compound. Transiently transfected cERG HEK-293 cell membranes (200µg/well), or stable hERG HEK-293 cell membranes (100µg/well) were incubated with twelve different concentrations of terfenadine and 5nM [^{3}H]-dofetilide for 90 minutes at room temperature. Total and non-specific binding were measured by incubating with 10% DMSO and 10µM unlabelled dofetilide to a total assay volume of 200µl. The membranes were harvested by filtration with a Packard Unifilter cell harvester and radioactivity (cpm) was measured. Two saturation experiments were carried out each for cERG and hERG expressing cell membrane samples. Each experiment was carried out in triplicate. Figure 5 shows the mean values of the experiments for each cell type (cERG or hERG transfected) and indicates that the IC_{50} for terfenadine is similar for cERG and hERG, being 77.2nM and 88.9nM respectively. IC_{20} values for terfenadine were 10.7nM and 12.3nM for canine and human ERG, respectively.

Example 8: Comparison of E4031 competition assay in HEK-293 cells transfected with cERG or hERG

The dofetilide binding assay was carried out using E4031 as the test compound. Transiently transfected cERG HEK-293 cell membranes (200µg/well) or stable hERG HEK-293 cell membranes (100µg/well) were incubated with twelve different concentrations of E4031 and 5nM [^{3}H]-dofetilide for 90 minutes at room temperature. Total and non-specific binding values were measured by incubation with 10% DMSO and 10µM unlabelled dofetilide in a total assay volume of 200µl. The membranes were harvested by filtration with a Packard Unifilter cell harvester and radioactivity (cpm) was measured. Two saturation experiments were carried out each for cERG and hERG expressing cell membrane samples. Each experiment was carried out in triplicate. Figure 6 shows the mean values of the experiments for each cell membrane type (cERG or hERG transfected) and indicates that the IC_{50} for E4031 is similar for cERG and hERG, being 27.3 nM and 35.4 nM respectively. IC_{20} values for E4031 were 3.8 nM and 4.9 nM for canine and human ERG, respectively.

When IC_{50} (or IC_{20}) values are compared for the compounds tested, they were found to be very similar for cERG and hERG. This indicates that either hERG or cERG can be used in the assay of the invention to predict the onset of QT prolongation in man.

Example 9: Further assay optimisation studies

To further optimise the assay for specific binding of dofetilide to homogenates of cell membrane containing hERG, the interaction of [^{3}H]-dofetilide with cell membrane preparations was examined in the SPA assay format using a Tris based buffer containing either KCl or $MgCl_2$. SPA assays were performed according to example 3 in 50mM Tris.Cl, 10mM KCl at pH7.4 or in 50mMTris.Cl, 1mM $MgCl_2$ at pH 7.4 as the assay buffer. Assays were performed using dofetilide or terodiline as the test compound. Comparison of specific binding detected in these buffer conditions revealed that specific binding was not observed when the assay buffer used was 50mMTris.Cl, 1mM $MgCl_2$ at pH 7.4; specific binding was observed in assay buffer consisting of 50mM Tris.Cl, 10mM KCl at pH7.4. For the assays carried out in 50mM Tris.Cl, 10mM KCl at pH7.4 as the assay buffer the IC_{50} and IC_{20} values were generated for each test

compound. The mean IC_{50} value for dofetilide was 8.69± 0.45nM, the mean IC_{50} value for terodiline was 1.87 ± 0.00 μM. The mean IC_{20} value for dofetilide was 1.2nM, the mean IC_{20} value for terodiline was 0.248μM.

Sequence Listing Information

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Claims

1. An assay comprising or consisting of the following steps:
(a) incubation of cells expressing ERG, or membranes derived from cells expressing ERG, or membranes derived from tissue expressing ERG, with labelled IKR blocker in assay buffer in the presence or absence of a test compound or a mixture of test compounds;
(b) determination of specifically bound labelled IKR blocker;
(c) calculation of the inhibition of labelled IKR blocker binding by the test compound or mixture of test compounds.
2. An assay according to claim 1, wherein the assay buffer is a Tris based buffer containing KCl.
3. An assay according to claim 2, wherein the assay buffer comprises or consists of from 30 to 100mM Tris.Cl, from 5 to 20mM KCl, and optionally from 0.6 to 2.0mM $MgCl_2$.
4. An assay according to claim 2, wherein the assay buffer comprises or consists of from 30 to 70mM Tris.Cl, from 6 to 15mM KCl, and optionally from 0.6 to 1.6mM $MgCl_2$.
5. An assay according to claim 2, wherein the assay buffer comprises or consists of from 40 to 60mM Tris.Cl, from 7.5 to 12.5mM KCl and optionally from 0.8 to 1.4mM $MgCl_2$.
6. An assay according to claim 2, wherein the assay buffer comprises or consists of from 45 to 55mM Tris.Cl, from 8.5 to 11.5mM KCl and optionally from 0.9 to 1.3 mM $MgCl_2$ or from 1.0 to 1.2mM $MgCl_2$.
7. An assay according to claim 2, wherein the assay buffer comprises or consists of 50mM Tris and 10mM KCl.
8. An assay according to claim 2, wherein the assay buffer comprises or consists of 50mM Tris, 10mM KCl and 1.0mM $MgCl_2$, or 50mM Tris, 10mM KCl and 1.2 mM $MgCl_2$.
9. An assay according to any one of the preceding claims wherein the assay buffer is at a pH between pH7.2 and pH7.6 at room temperature.
10. An assay according to claim 9, wherein the assay buffer is at pH7.4.
11. An assay according to any one of the preceding claims wherein the ERG is human ERG.

12. An assay according to any one of the preceding claims, wherein the labelled IKR blocker is labelled dofetilide or labelled MK-499.

13. An assay according to claim 12, wherein the labelled dofetilide or labelled MK-499 is radiolabelled.

14. An assay according to claim 13, wherein the radiolabel is tritium (^3H).

15. An assay according to any one of the preceding claims having the following additional step(s):

(d) calculation of the IC_{20} for the test compound or mixture of test compounds, and optionally,

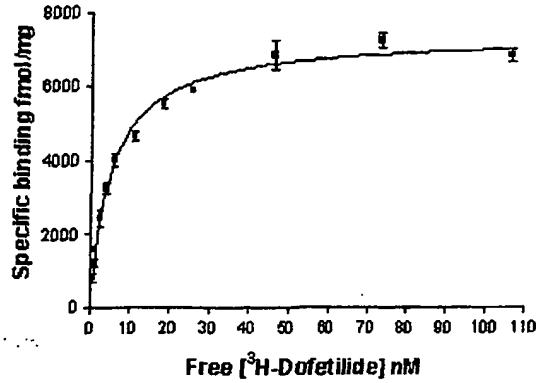
(e) comparison of the IC_{20} value of the test compound or mixture of test compounds with the concentration required for the desired therapeutic effect of the compound in vivo.

16. An assay according to any one of the preceding claims wherein the assay is performed as a filter binding assay.

17. An assay according to any one of claims 1 to 15 wherein the assay is performed as a scintillation proximity assay.

Figure1

(a)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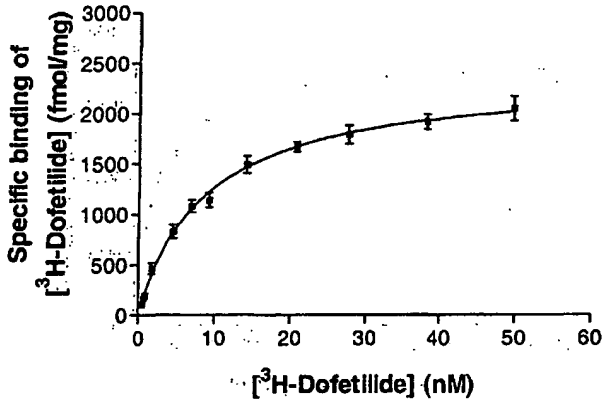
(b)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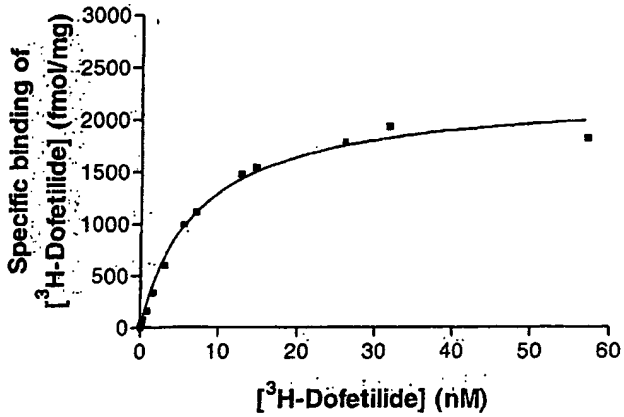
2500
2000
1500
1000
500
0
0 10 20 30 40 50 60
[3H-Dofetilide] (nM)

(c)


Specific binding of [3H-Dofetilide] (fmol/mg)
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2000
1500
1000
500
0
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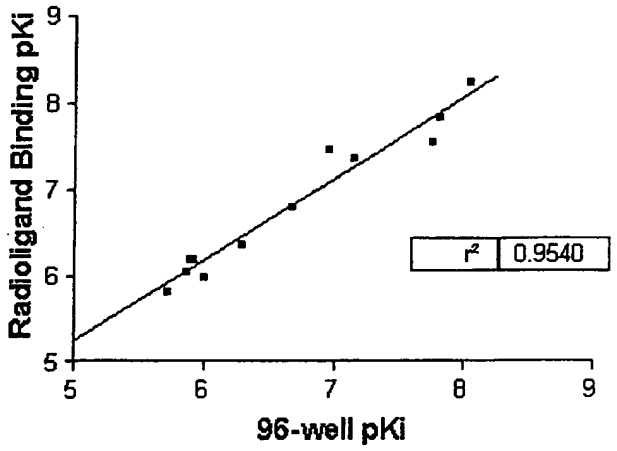
[3H-Dofetilide] (nM)

Figure 2

(a)



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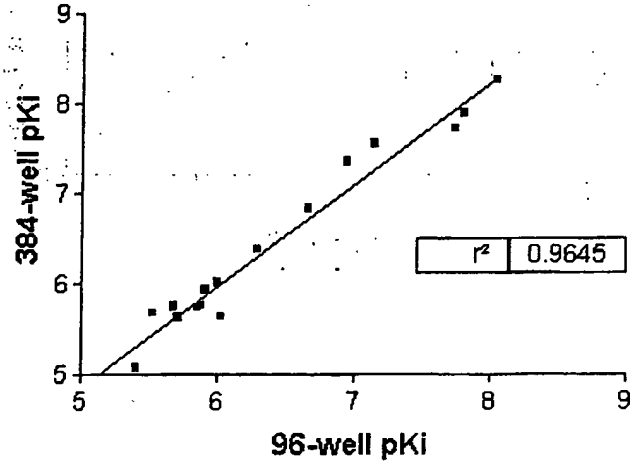
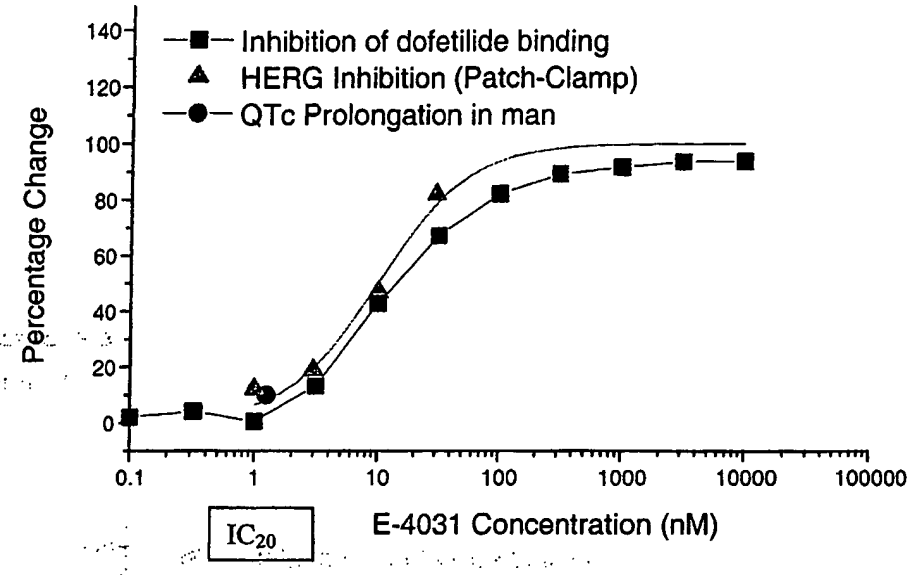


Figure 3

(a)


Inhibition of dofetilide binding
HERG Inhibition (Patch-Clamp)
QTc Prolongation in man
Percentage Change
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100
80
60
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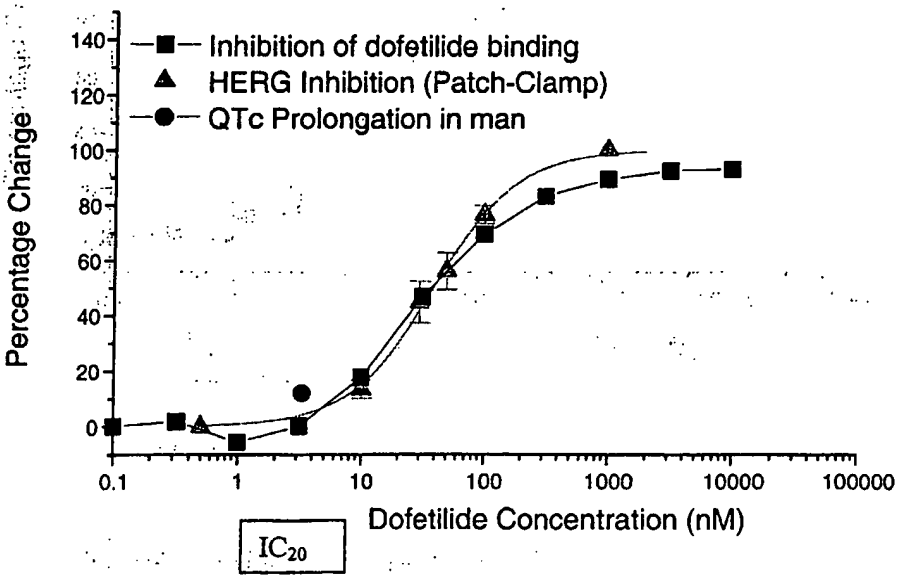
1
10
100
1000
10000
100000
IC20
E-4031 Concentration (nM)

(b)


Inhibition of dofetilide binding
HERG Inhibition (Patch-Clamp)
QTc Prolongation in man
Percentage Change
140
120
100
80
60
40
20
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0.1
1
10
100
1000
10000
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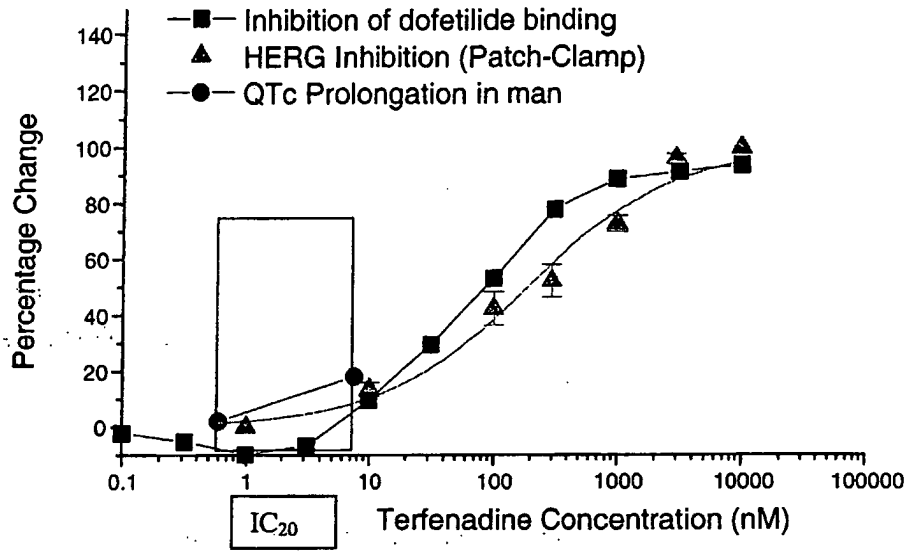
IC20
Dofetilide Concentration (nM)

Figure 3 continued

(c)



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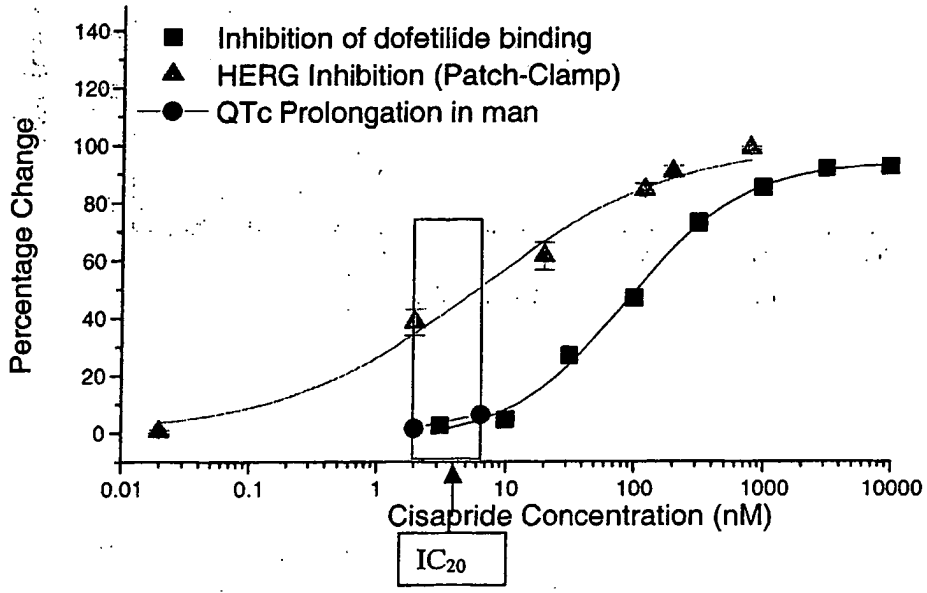


Figure 4

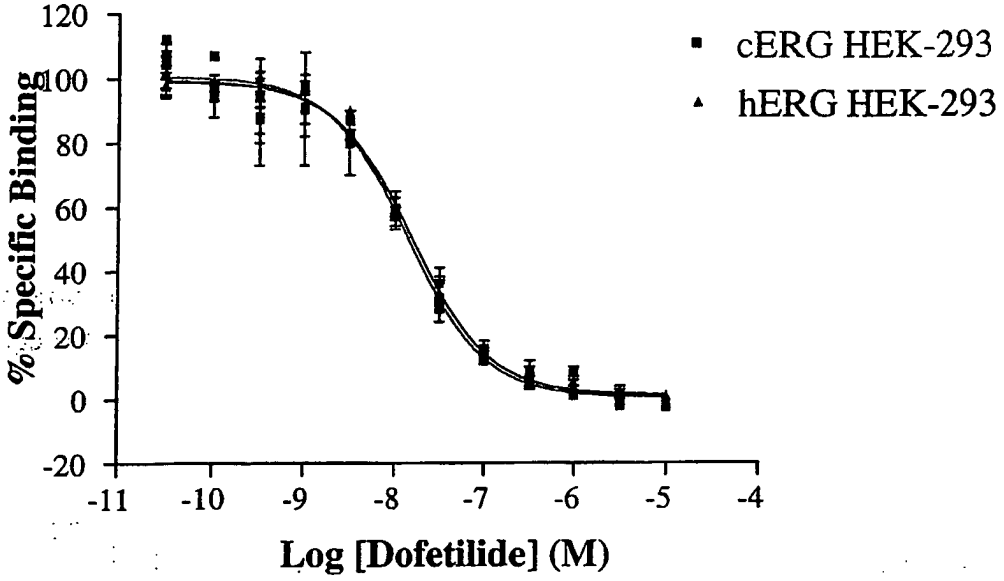

120
100
80
60
40
20
0
-20
% Specific Binding
-11
-10
-9
-8
-7
-6
-5
-4
Log [Dofetilide] (M)
cERG HEK-293
hERG HEK-293

Figure 5

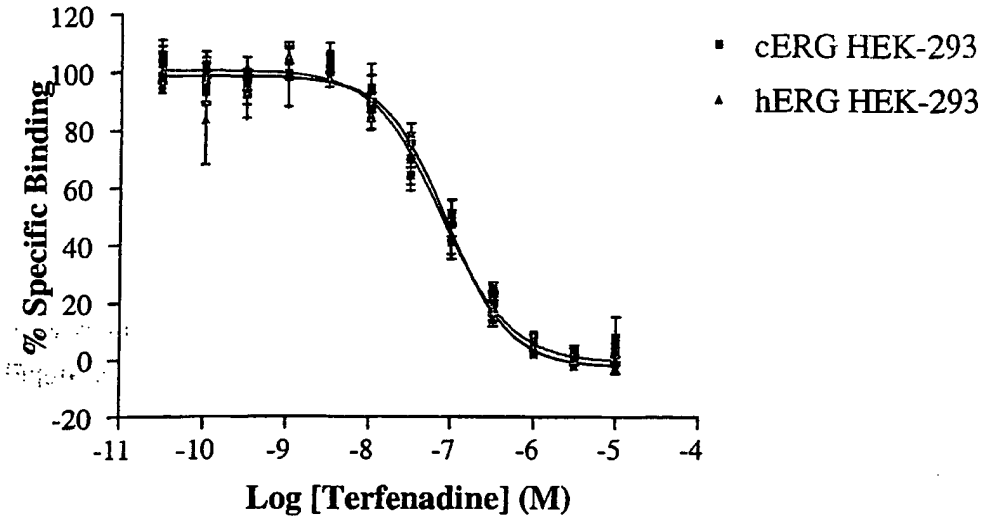
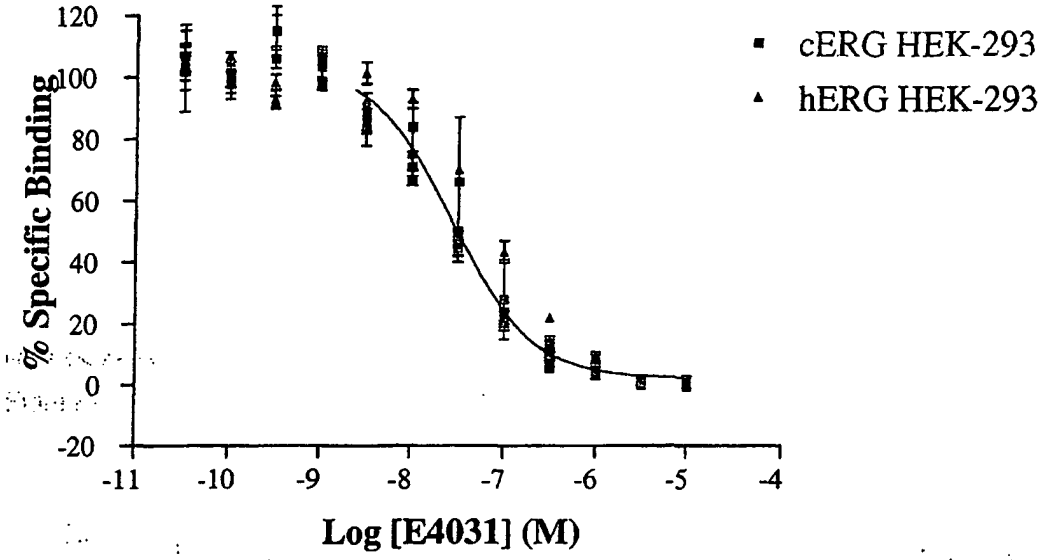


Figure 6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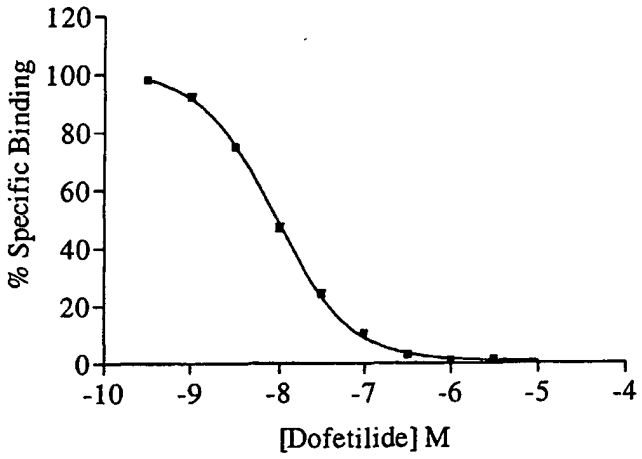
hERG HEK-293

Figure 7

(a)



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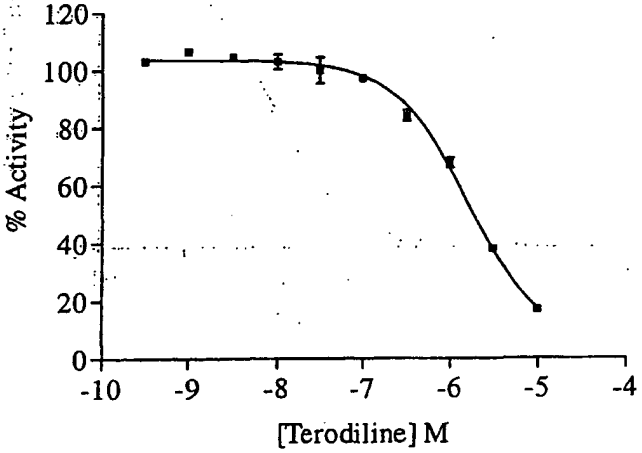

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<110> Pfizer Inc (CA, EP except EP(GB), JP, US.) Pfizer Ltd (EP(GB)).

<120> Assay

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<151> 2001-09-04

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<151> 2001-09-20

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(74) Agents: **OSBORNE, David, W.** et al.; Thorpe North & Western LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).

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(54) Title: DRUG DELIVERY SYSTEM FOR TREATING URINARY INCONTINENCE

(57) Abstract: Methods for the prevention or amelioration of urinary incontinence are disclosed and described. One method includes the coadministration of an anticholinergic agent with either an SSRI, or an SNRI, or both.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/27409

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 13/00
US CL : 424/449, 443

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)
U.S. : 424/449, 443

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0010216 A1 (ROGOSKY et al.) 24 January 2002 (24.01.2002), abstract; page 1: 0012; page 3: 0033, 0035, 0037, 0039.	1-21, 23-32

☐ 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 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
11 February 2004 (11.02.2004)

Date of mailing of the international search report
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Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/27409

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 22
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:
Claim 22 depends on claim 20, which is reciting a transdermal patch; meanwhile the claim is directed to composition in the oral form.

3. ☐ Claim 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.

Continuation of B. FIELDS SEARCHED Item 3:
WEST:ALL DATA BASES:
Search terms: transdermal, oral, oxybutynin, tolterodine, fluoxetine, paroxetine.

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(54) Title: IMPROVED DRUG DELIVERY SYSTEM FOR TREATMENT OF URINARY INCONTINENCE

(57) Abstract: Methods for the prevention or amelioration of urinary incontinence are disclosed and described. One method includes the coadministration of an anticholinergic agent with either an SSRI, or an SNRI, or both.

IMPROVED DRUG DELIVERY SYSTEM FOR TREATMENT OF URINARY INCONTINENCE

PRIORITY DATA

This application claims priority to United States Provisional Patent Application Serial no. 60/407,009, filed on August 30, 2002, which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to coadministration of an anticholinergic agent with either a selective serotonin reuptake inhibitor (SSRI) or a selective norepinephrine reuptake inhibitor (SNRI), or both, for the treatment of urinary incontinence. Accordingly, this invention covers the fields of pharmaceutical sciences, medicine and other health sciences.

BACKGROUND OF THE INVENTION

Recently, an effective transdermal medication has been developed for the treatment of what has come to be known as overactive bladder which is ocassioned by an incontinence. Urge incontinence results from instability of the detrusor muscle, the muscle surrounding the bladder. The cholinergic receptors of the detrusor can be over-stimulated causing spasmodic contractions and a sensation of urgency to urinate, which may lead to an urgency to urinate, an increased micturation rate, and in extreme cases to incontinent episodes.

An oral sustained release technology is exemplified by Guittard et al., U.S. Patent 6,262,115 (Alza) discloses tablets of oxybutynin without any further pharmaceutical component which has hydroxypropylmethylcellulose present in a molecular weight of approximately 10,000 (herein: Guittard). An effective transdermal delivery system has been developed by Watson Pharmaceuticals, Inc., which comprises technology disclosed in Quan et al., U.S. Patent 5,834,010 (1998) (herein: "Quan"). Quan discloses transdermal technology for the delivery of oxybutynin. This application incorporates by reference in toto the complete disclosure of Quan. Quan teaches a transdermal medication that can be applied typically for twenty-four hours. It is recommended that such a transdermal medication be applied after a morning shower or bath, to thereby provide a twenty-four hour period of

protection against such overactive bladder condition until the following morning. Other attempts to provide a treatment in this area include Pharmacia PCT application 0162236 with U.S. priority of February 24, 2000, and Waki et al., European Patent Application 1174132 (2002). Waki et al. provide a recent time slice of the state of the art: "[T]he countermeasure for the bladder functional disorder such as urinary incontinence or pollakiuria associated with the increase in the population of the advanced age group is one of the most important question of vital interest in the medical treatment. Therefore, the development of the effective drugs in treating urinary incontinence or pollakiuria are to be desired, and various medicines in addition to oral drugs already available in the market are on their way to development. Oxybutynin hydrochloride used in the treatment of urinary incontinence and pollakiuria is well recognized as the excellent anticholinergic drug demonstrating its pharmacological effect through acetylcholine antagonism. An oral dosage form of the drug requires a comparatively small quantity of 2-3 mg per dose, but they have to be taken three times a day. In addition, the absorption of the drug through the intestinal tract is known to be good, but the higher hepatic metabolism is also reported (Pharmacopoeia 4 (5), 45-53, 1990). Regarding the routes of administration, the oral form has the advantage in not giving pain to patients as compared with the injection form, but it may not be easy to administer the medicine which has to be taken at the regular interval for the aged patients who may sometimes require the medical helper. Furthermore, the drug taken orally is inevitably absorbed into a hepatoportal vein through the intestinal tract, thereby being subjected to the first pass effect termed for the intense hepatic metabolism of the drug on its first passage and often leads to the marked decrease in biological availability in many cases. In order to maintain the effective concentration of the drug in the blood, it is necessary to administer a relatively large dose of drug, and as a result, an incidence in adverse effects naturally increases. From these standpoints, there is the urgent need for the development, of a preparation that is relatively easy to administer, long lasting in its effect, and yet with fewer adverse effects. In view of pharmacokinetics, a preparation that does not exhibit the behavior of a transitory drug concentration in the blood such that the blood concentration rapidly increases and then decreases as often observed in the general orally administrated preparation, but whose concentration increases gradually and its effective concentration in the blood can be continuously maintained over a long period of time is highly desired."

In an embodiment of the invention that utilizes the Quan technology, in such an embodiment, the matrix patch comprises about 0.1% to about 50% by weight triacetin, more preferably about 1% to about 40% by weight triacetin, and most preferably about 2% to about 20% by weight triacetin. The polymer layer is preferably an adhesive, but can also be laminated to an adhesive layer or used with an overlay adhesive. Suitable polymers include acrylics, vinyl acetates, natural and synthetic rubbers, ethylenevinylacetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized weight polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof. Acrylic copolymer adhesives are preferred. The matrix patch can also contain diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof provided that such additives do not alter the basic characteristics of the matrix patch.

In aspects of the invention utilizing the Quan technology, suitable polymers that can be used in the biocompatible polymeric layer of the matrix patch include pressure-sensitive adhesives suitable for long-term contact with the skin. Such adhesives must be physically and chemically compatible with the drug and enhancer, and with any carriers and/or vehicles or other additives incorporated into the drug/enhancer composition. Suitable adhesives for use in the matrix patch include acrylic adhesives including cross-linked and uncross- linked acrylic copolymers; vinyl acetate adhesives; natural and synthetic rubbers including polyisobutylenes, neoprenes, polybutadienes, and polyisoprenes; ethylenevinylacetate copolymers; polysiloxanes; polyacrylates; polyurethanes; plasticized weight polyether block amide copolymers, and plasticized styrene-rubber block copolymers. Preferred contact adhesives for use in the matrix patch herein are acrylic adhesives, such as TSR (Sekisui Chemical Co., Osaka, Japan) and DuroTak. RTM. adhesives (National Starch & Chemical Co., Bridgewater, N.J.), and polyisobutylene adhesives such as ARcare.TM. MA-24 (Adhesives Research, Glen Rock, Pa.).

In use, the matrix patch contains a distal backing laminated on the polymer layer. The distal backing defines the side of the matrix patch that faces the environment, i.e., distal to the skin or mucosa. The backing layer functions to protect the matrix polymer layer and drug/enhancer composition and to provide an impenetrable layer that prevents loss of drug to the environment. Thus, the material chosen for the backing should be compatible with the polymer layer, drug, and enhancer, and should be minimally permeable to any components of the matrix patch.

Advantageously, the backing can be opaque to protect components of the matrix patch from degradation from exposure to ultraviolet light. Further, the backing should be capable of binding to and supporting the polymer layer, yet should be pliable to accommodate the movements of a person using the matrix patch. Suitable materials for the backing include metal foils, metalized polyfoils, composite foils or films containing polyester such as polyester terephthalate, polyester or aluminized polyester, polytetrafluoroethylene, polyether block amide copolymers, polyethylene methyl methacrylate block copolymers, polyurethanes, polyvinylidene chloride, nylon, silicone elastomers, rubber-based polyisobutylene, styrene, styrene-butadiene and styrene- isoprene copolymers, polyethylene, and polypropylene. A thickness of about 0.0005 to 0.01 inch is preferred. The release liner can be made of the same materials as the backing, or other suitable films coated with an appropriate release surface.

The matrix patch can further comprise various additives in addition to the polymer layer, basic drug, and triacetin-containing penetration enhancer that are the fundamental components of the transdermal drug delivery system. These additives are generally those pharmaceutically acceptable ingredients that are known in the art of drug delivery and, more particularly, in the art of transdermal drug delivery provided that such additive ingredients do not materially alter the basic and novel characteristics of the matrix patch. For example, suitable diluents can include mineral oil, low molecular weight polymers, plasticizers, and the like. Many transdermal drug delivery formulations have a tendency to cause skin irritation after prolonged exposure to the skin, thus addition of a skin irritation reducing agent aids in achieving a composition that is better tolerated by the skin. A preferred skin irritation reducing agent is glycerin, U.S. Pat. No. 4,855,294.

The matrix patch device containing a polymer layer, the drugs, and triacetin-containing penetration enhancer is brought in contact with the skin or mucosa at a selected application situs and is held in place by a suitable pressure-sensitive adhesive. Preferably, the polymer layer of the matrix patch is an adhesive, but the polymer layer can also be laminated to an adhesive layer or used with an overlay adhesive.

While Quan provides an excellent medication for cases of overactive bladder for most patients, an improvement is contemplated in the present invention for post-menopausal women.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with a greater resistance to active bladder reaction via the coadministration of a therapeutically effective amount of an anticholinergic agent with a therapeutically effective amount of an SSRI, or SNRI, or both. In one aspect, the anticholinergic agent may be oxybutynin and the SSRI may be fluoxitine.

There has thus been outlined, rather broadly, the more important features of the invention so that the detailed description thereof that follows may be better understood, and so that the present contribution to the art may be better appreciated. Other features of the present invention will become clearer from the following detailed description of the invention, taken with the accompanying claims, or may be learned by the practice of the invention.

DETAILED DESCRIPTION

Accordingly, there are several specific aspects of the present invention. In a first embodiment, there is provided an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of FLUOXETINE whereby there is an enhanced resistance to said active bladder reaction.

In an aspect of this first embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In a second aspect of the invention, an improvement is provided in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction. In an embodiment, said coadministration is

provided orally, and in a further embodiment thereunder, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In an alternative embodiment of this aspect of the inventionsaid coadministration is from a transdermal patch.

In a third aspect of the invention, an improvement is provided in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction. In an aspect of this embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In a fourth aspect of the invention there is provided an improvement in the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction. In an aspect of this embodiment, said coadministration is provided orally. In a still further aspect, the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction. In a further aspect, said coadministration is from a transdermal patch.

In further aspects of the invention, oral and transdermal delivery systems are provided for each of the aspects of the invention set forth above.

The range of drugs in the composition of the invention will vary within amounts necessary to provide the desired effect of a prophylaxis or treatment of urinary incontinence in post-menopausal women with weakened musculature in the area of the urinary tract.

In oral formulation embodiments of the invention with oxybutynin it is contemplated that oxybutynin will be used in the form of its hydrochloride .

In sustained release formulations with any of oxybutynin, Tolterodine, Fluoxetine and Paroxetine, it is contemplated that twice the dosage will be provided

vis a vis a regular (non-sustained release) tablet.

For Fluoxetine, the amount should vary from about 5 to about 120 mg. per dosage; in an embodiment, the range is 10 to 80 mg., and in an example the amount is 40 mg. A blood level that is continuously achieved for most of the period of delivery is to be achieved in accordance with the invention which should be from about 15 to 55 nanograms/ml;

For Paroxetine, the amount should vary from about 5 to 60 mg. per dosage unit; in an embodiment, the amount varies from about 10 to about 40 mg., and in a preferred embodiment the amount is 30 mg.

For oxybutynin or Tolterodine the amount is generally from about 2.5 to about 20 mg., and in an embodiment the amount is from about 5 to about 15 mg., whilst in an example the amount is 10 mg.

Hydroxypropylmethyl cellulose may be replaced with other sustained release vehicles. The amount and viscosity of each should be selected to provide a sustained release of the drug over a period of 24 hours.

The improvement of the invention in all aspects provides a post-menopausal woman with a protection against unwanted urination due to the frequent loss of muscle or sphinter control that accompanies the female aging process. A common example of this problem is leakage following a sneeze or a cough.

EXAMPLE I:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 3.9 mg. oxybutynin and 20 mg. fluoxetine.

The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the fluoxetine.

EXAMPLE II:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 3.9 mg. oxybutynin and 20 mg. paroxetine. The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the paroxetine.

EXAMPLES III-IV:

Oral sustained release technology is exemplified by Guitard Example 1 which

discloses "[a] therapeutic oxybutynin composition for administering to a patient *** prepared as follows: First, 103 grams of oxybutynin hydrochloride was dissolved in 1200 ml (milliliters) of anhydrous ethanol. Separately, 2,280 g of polyethylene oxide of 200,000 weight-average molecular weight, 150 g of hydroxypropylmethylcellulose of 9,200 average-number molecular weight and 450 g of sodium chloride were dry blended in a conventional blender for 10 minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution was added slowly to the blend, with the blender continuously blending until all the ingredients were added to the three component dry blend, with the blending continued for another 8 to 10 minutes. The blended wet composition was passed through a 16 mesh screen and dried overnight at a room temperature of 72[deg] F. (22.2[deg]). Then, the dry granules were passed through a 20 mesh screen, 18 g of magnesium stearate was added, and all the ingredients blended again for 5 minutes. The fresh granules are ready for formulation into a therapeutic oxybutynin composition. The therapeutic composition comprises 3.4 wt % oxybutynin hydrochloride, 76 wt % polyethylene oxide of 200,000 weight-average molecular weight, 5 wt % of hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 15 wt % sodium chloride, and 0.6 wt % magnesium stearate." In accordance with the present invention, a sustained release tablet is provided by doubling the amounts of the two drug ingredients of Example I and II and incorporating this combination of drugs in place of the oxybutynin of Example 1 of Guittard. Each of the two tablets provides a 24 hour period of relief for incontinence.

EXAMPLE V:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 4.0 mg. Tolterodine and 20 mg. fluoxetine.
The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the fluoxetine.

EXAMPLE VI:

Using conventional tablet excipients and techniques, a rapidly dissolving tablet is provided which contains 4.0 mg. Tolterodine and 20 mg. paroxetine.
The tablet provides a mature, post-menopausal woman with enhanced relief against incontinence vis a vis a tablet without the paroxetine.

EXAMPLES VII-VIII:

Using the sustained release technology of Examples III-IV, a sustained release tablet is provided by doubling the amounts of the two drug ingredients of Example V and VI and otherwise following the procedure used in Examples III-IV. Each of the two tablets provides a 24 hour period of relief for incontinence.

EXAMPLE IX:

As a control, Example 1 of Quan is set forth: "Oxybutynin free base, pKa=10.3, is a strongly basic drug administered transdermally for antispasmodic and anticholinergic therapy. Matrix patches containing varying amounts of oxybutynin free base and penetration enhancers were prepared and tested as described above. The matrix systems consisted of 5 to 20% by weight of oxybutynin free base and 0 to 20% by weight of the enhancer contained in a medical grade acrylic copolymer adhesive.

"The matrix formulations were prepared as follows. First, the solids content of the adhesive was determined by weighing a small amount of the adhesive solution in a preweighed aluminum dish. The solvent was evaporated by overnight drying in a convection oven maintained at 80. degree. C. and the weight of the residue (dry adhesive) and percent solid adhesive content of the solution were determined. Once the solids content was determined, a known weight of the acrylic copolymer adhesive solution was weighed into a glass bottle. From the weight of the adhesive solution and the percent solid adhesive content, the amount of adhesive in the solution was calculated. Oxybutynin free base and enhancer were added to the bottle in proportions to yield the selected final composition. The bottle was then tightly capped, sealed with laboratory film, and rotated overnight until all ingredients had completely dissolved and the resultant solution was visually clear.

"Approximately 8 ml of the solution was then dispensed on a silanized polyester release liner and cast with a 10 mil gap casting knife. The casting was then dried in a convection oven at 70.degree. C. for 15 minutes to evaporate the solvent and to yield a dried film approximately 0.002 inch thick. A 0.003 inch thick polyethylene backing film was laminated onto the dried adhesive film with a rubber roller. These matrix laminates were then used to conduct in vitro skin flux studies that showed satisfactory results as explained in Table 1 of Quan.".

The transdermal matrix for the delivery of oxybutynin of Example 1 of Quan

is modified by incorporating therein 40 mg. of fluoxetine. Comparable results are achieved to those of Quan for patients other than post-menopausal women where the present invention provides a better retardation of active bladder response based upon weakened musculature.

EXAMPLE X:

The transdermal matrix for the delivery of oxybutynin of Example 1 of Quan is modified by incorporating therein 40 mg. of paroxetine. Comparable results are achieved to those of Quan for patients other than post-menopausal women where the present invention provides a better retardation of active bladder response based upon weakened musculature.

EXAMPLES XI-XII:

By replacing an equal amount of Tolterodine for the oxybutynin of Examples XIII and IX, a transdermal medication particularly suited for post-menopausal women is achieved that is designed to provide superior relief against active bladder caused by a weakened musculature.

EXAMPLES XIII:

The Waki et al. application discloses that "1.0 part of oxybutynin hydrochloride was dissolved in 200.0 parts of isoprapanol as the solvent, and then 20.0 parts of N-vinyl acetamide copolymer (PNVA GE167, a product of Showa Denko K.K.), 1.0 part of synthetic aluminum silicate and 1.0 part of borax were added and stir-mixed. The mixture solution containing 62.0 parts of glycerin and 15.0 parts of propylene glycol were added and continuously stirred.

"The solvent-type plaster with the desirable viscosity for the plaster is spread out over the non-woven fabric, then solvent is removed by heat drying (solvent drying) and the strippable film made of polyester was adhered. This was cut into the desirable size to obtain the transdermal absorption preparation containing oxybutynin hydrochloride."

By replacing the oxybutynin of the quoted Waki example with a combination of each of the drugs as set forth in Examples XIII-XI, a superior overall medication is contemplated for post-menopausal women with a weakened musculature.

CLAIMS

What is claimed is:

1. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of FLUOXETINE whereby there is an enhanced resistance to said active bladder reaction.

2. The method of claim 1 wherein said coadministration is provided orally.

3. The method of claim 2 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

4. The method of claim 1 wherein said coadministration is from a transdermal patch.

5. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

6. The method of claim 6 wherein said coadministration is provided orally.

7. The method of claim 7 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

8. The method of claim 5 wherein said coadministration is from a transdermal patch.

9 In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which

comprises the coadministration therewith of an effective amount of fluoxetine whereby there is an enhanced resistance to said active bladder reaction.

10. The method of claim 9 wherein said coadministration is provided orally.

11. The method of claim 10 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

12. The method of claim 11 wherein said coadministration is from a transdermal patch.

13. In the method of providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of Tolterodine, the improvement which comprises the coadministration therewith of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

14. The method of claim 13 wherein said coadministration is provided orally.

15. The method of claim 14 wherein the oral administration is via a sustained release vehicle to provide a 24 hour period of relief from active bladder reaction.

16. The method of claim 13 wherein said coadministration is from a transdermal patch.

17. A composition suitable for providing a post-menopausal female patient with a weakened musculature in the area of the urinary tract with an improved resistance to active bladder reaction via the oral delivery of oxybutynin, the improvement which comprises the providing a dosage form for the administration of an effective amount of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

18. The composition of claim 17 in oral form.

19. The composition of claim 18 in a sustained release vehicle to provide a 24

of paroxetine whereby there is an enhanced resistance to said active bladder reaction.

30. The composition of claim 29 in oral form.

31. The composition of claim 29 in a sustained release vehicle to provide a 24 hour delivery to the patient.

32. A transdermal patch containing the medication of claim 29.

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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/201,756	08/10/2005	Claus Meese	12961/46103

CONFIRMATION NO. 3812

26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY10004

Title: Novel derivatives of 3,3-diphenylpropylamines

Publication No. US-2006-0270738-A1
Publication Date: 11/30/2006

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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Pre-Grant Publication Division, 703-605-4283

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	407	514/551 or 560/140	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/15 07:59
L2	✓ 8	l1 and (diphenylpropylamines or tolterodine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2007/04/15 09:36
L3	1	("5382600").PN.	USPAT	OR	OFF	2007/04/15 08:21
L4	1	("6858650").PN.	USPAT	OR	OFF	2007/04/15 09:36

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 NEWS  6  DEC 18  MEDLINE updated in preparation for 2007 reload
 NEWS  7  DEC 27  CA/CAplus enhanced with more pre-1907 records
 NEWS  8  JAN 08  CHEMLIST enhanced with New Zealand Inventory of Chemicals
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                  multiple databases
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 NEWS 22  FEB 26  IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 23  FEB 26  CAS Registry Number crossover limit increased from 10,000
                  to 300,000 in multiple databases
 NEWS 24  MAR 15  WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 25  MAR 16  CASREACT coverage extended
 NEWS 26  MAR 20  MARPAT now updated daily
 NEWS 27  MAR 22  LWPI reloaded
 NEWS 28  MAR 30  RDISCLOSURE reloaded with enhancements
 NEWS 29  MAR 30  INPADOCDB will replace INPADOC on STN
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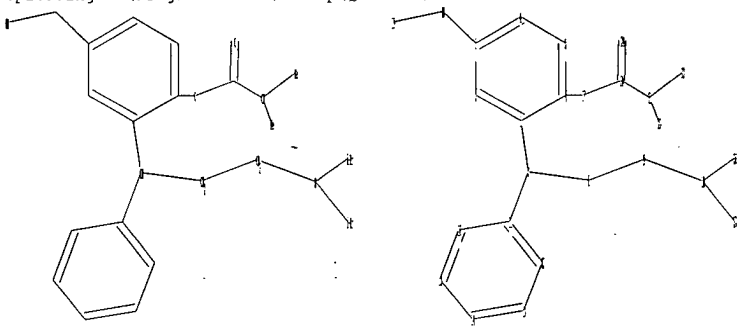

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11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS
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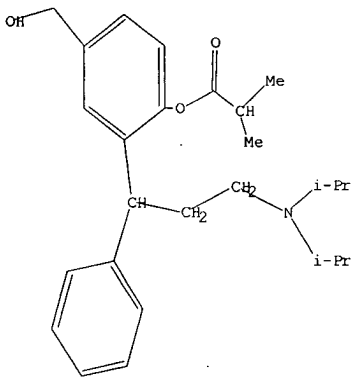

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BATCH **COMPLETE**
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PROJECTED ANSWERS: 0 TO 0

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L4 17 L3

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L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:259675 CAPLUS
DOCUMENT NUMBER: 146:281054
TITLE: Pharmaceutical compositions comprising combinations of an antimuscarinic agent and an anticholinergic agent for the treatment of a patient suffering from overactive bladder
INVENTOR(S): Paborji, Mehdi
PATENT ASSIGNEE(S): Theravida, LLC, USA
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007027675	A1	20070308	WO 2006-US33671	20060828

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2007053995 A1 20070308 US 2006-467760 20060828

PRIORITY APPLN. INFO.: US 2005-714150P P 20050902

PATE IS NO GOOD, DIFF. ASSIGNEE - NO ODP.

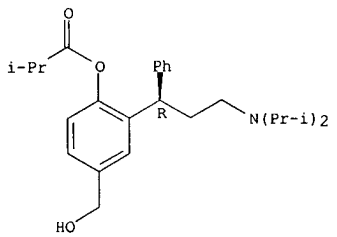
AB Disclosed herein are pharmaceutical compns. comprising various combinations of an antimuscarinic or an anticholinergic agent, a compound that causes stimulation of salivary glands, and a compound that relieves constipation. Also disclosed are methods of treating a patient suffering from overactive bladder comprising administering to the patient the above pharmaceutical composition To an individual with overactive bladder is given 5 mg of oxybutynin two to four times a day in addition to 5 mg of pilocarpine two or three times a day. If the individual continues to complain about dry mouth, the dose of pilocarpine is increased to 10 mg two or three times a day. The dose can be increased upto 20 mg, or 50 mg, if needed. Each dose of oxybutynin can be increased to 10, 15, 20, or 30 mg.

IT 286930-02-7, Fesoterodine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy for treatment of disease)

RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1133705 CAPLUS

DOCUMENT NUMBER: 146:74422

TITLE: Treatment of the overactive bladder syndrome with muscarinic receptor antagonists - a matter of metabolites?

AUTHOR(S): Michel, Martin C.; Hegde, Sharath S.

CORPORATE SOURCE: Department of Pharmacology & Pharmacotherapy, Academic Medical Center, University of Amsterdam, Amsterdam, 1105 AZ, Neth.

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2006), 374(2), 79-85

CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

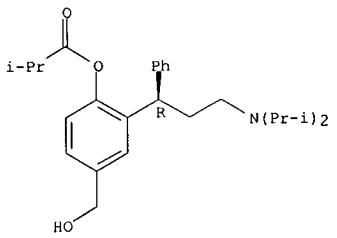
AB A review. Antagonists of muscarinic acetylcholine receptors, such as darifenacin, oxybutynin, propiverine, solifenacin, tolterodine, and trospium, are the mainstay of the treatment of the overactive bladder syndrome. Fesoterodine is a newer drug awaiting regulatory approval. The authors briefly review the pharmacol. activity of their metabolites and discuss how active metabolites may contribute to their efficacy and tolerability in vivo. Except for trospium, and perhaps solifenacin, all of the above drugs form active metabolites, and their presence and activity need to be taken into consideration when elucidating relationships between pharmacokinetics and pharmacodynamics of these drugs. Moreover, the ratios between parent compds. and metabolites may differ depending on genotype of the metabolizing enzymes, concomitant medication, and/or drug formulation. Differential generation of active metabolites of darifenacin or tolterodine are unlikely to influence the overall clin. profile of these drugs in a major way because the active metabolites exhibit a similar pharmacol. profile as the parent compound In contrast, metabolites of oxybutynin and propiverine may behave quant. or even qual. differently from their parent compds. and this may have an impact on the overall clin. profile of these drugs. The authors conclude that more comprehensive studies of drug metabolites are required for an improved understanding of their clin. effects.

IT 286930-02-7, Fesoterodine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of overactive bladder syndrome with muscarinic receptor antagonists - a matter of metabolites)

RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:630212 CAPLUS

DOCUMENT NUMBER: 145:110309

TITLE: Injectable sustained release microspheric preparation of 3,3-diphenylpropylamine derivatives as muscarinic receptor antagonists

INVENTOR(S): Li, Youxin

PATENT ASSIGNEE(S): Peop. Rep. China

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006066509	A1	20060629	WO 2005-CN2277	20051222
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CN 1795845	A	20060705	CN 2004-10101721	20041223
PRIORITY APPLN. INFO.:			CN 2004-10101721 A	20041223

OTHER SOURCE(S): MARPAT 145:110309
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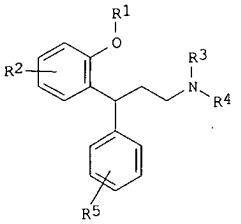
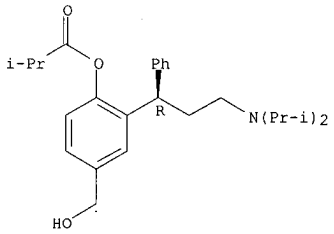


I

AB The invention relates to injectable sustained release microspheric preparation of 3,3-diphenylpropylamine, its preparing process and application. The said sustained release microspheric preparation consists of 3,3-diphenylpropylamine of formula I as follows, its optical enantiomers or racemates and one or more medicinal biodegradable high-mol. auxiliary material and other medicinal auxiliary material, wherein the definition of R1, R2 R3 R4 and R5 sees the claims. The injectable sustained release microspheric preparation according to the invention is used for treatment or supplementary treatment of diseases related to the muscarinic receptor and unstable or overactive bladder such as urgency or stress urinary incontinence, urge incontinence, urinary urgency or frequency, etc.

IT 286930-02-7
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable sustained release microspheric preparation of 3,3-diphenylpropylamine derivs. as muscarinic receptor antagonists)
RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:76147 CAPLUS
DOCUMENT NUMBER: 144:156740
TITLE: Combinations of statins with bronchodilators for treatment of respiratory disorders
INVENTOR(S): Lindmark, Bertil; Thoren, Anders Ingemar
PATENT ASSIGNEE(S): AstraZeneca AB, Swed.; AstraZeneca UK Limited
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

DIFF. ASSIGNEE, DATE IS NO GOOD

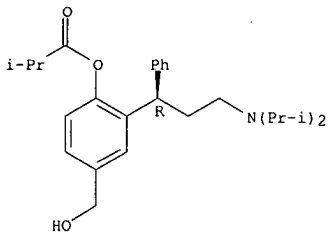
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006008437	A1	20060126	WO 2005-GB2413	20050620
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005263883	A1	20060126	AU 2005-263883	20050620
CA 2573393	A1	20060126	CA 2005-2573393	20050620
PRIORITY APPLN. INFO.:			GB 2004-15789 A	20040715
			WO 2005-GB2413 W	20050620

AB The invention provides medicaments comprising combinations of bronchodilators, glucocorticosteroids and HMG-CoA reductase inhibitors in the treatment of respiratory disorders such as chronic obstructive pulmonary disease (COPD). For example, a metered dose inhaler contained per dose formoterol fumarate dihydrate 4.5 μg, budesonide 160 μg, rosuvastatin 1 mg, and HFA 227 50 μL. Also, an inhalation/oral combination comprised an aerosol formulation containing per dose formoterol fumarate dihydrate 4.5 μg and budesonide 160 μg, and a tablet formulation containing rosuvastatin 10 mg.

IT 286930-02-7, Fesoterodine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of statins with bronchodilators for treatment of respiratory disorders)
RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1075634 CAPLUS
DOCUMENT NUMBER: 143:373316
TITLE: Combination therapy using adrenergic receptor antagonist in combination with muscarinic receptor antagonists and testosterone 5-reductase inhibitors for lower urinary tract symptoms
INVENTOR(S): Chugh, Anita; Tiwari, Atul
PATENT ASSIGNEE(S): Ranbaxy Laboratories Limited, India
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

NOT PRIOR ART

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092341	A1	20051006	WO 2004-IB842	20040322
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1746998	A1	20070131	EP 2004-722336	20040322
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, LT, LV, MK				
WO 2005092342	A1	20051006	WO 2004-IB866	20040323
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

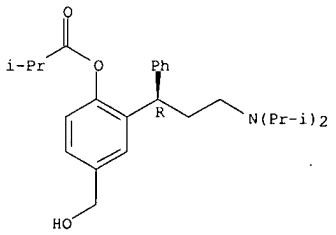
PRIORITY APPLN. INFO.: WO 2004-IB842 W 20040322

AB This invention relates to combination therapy for the treatment of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) associated with or without BPH. The combination therapy comprises of 1α adrenergic receptor (AR) subtype selective antagonist in combination with muscarinic receptor antagonist and optionally included Testosterone 5-reductase inhibitor for relief of LUTS in a subject with or without BPH.

IT 286930-02-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy using adrenergic receptor antagonist in combination with muscarinic receptor antagonists and testosterone 5-reductase inhibitors for lower urinary tract symptoms)

RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:902168 CAPLUS
DOCUMENT NUMBER: 141:374727
TITLE: Method using quaternary ammonium compounds for the treatment of irritable bowel syndrome
INVENTOR(S): Richards, Ivan Michael; Kolbasa, Karen Patrice
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, LLC, USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

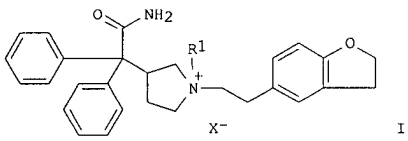
DIFF. ASSIGNEE, DATE IS NO GOOD.

NOT PRIOR ART AND NO ODP.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004091597	A2	20041028	WO 2004-IB1218	20040405
WO 2004091597	A3	20050414		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,				

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004220224 A1 20041104 US 2004-823944 20040413
PRIORITY APPLN. INFO.: US 2003-462921P P 20030415
OTHER SOURCE(S): MARPAT 141:374727
GI



I

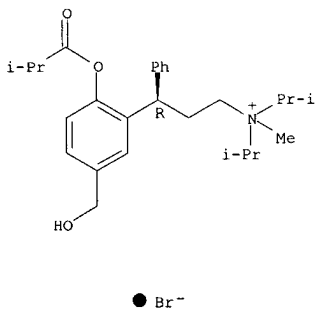
AB The invention discloses a method for treating irritable bowel syndrome by administering quaternary ammonium compds. Compds. of the invention include e.g. I [R1 = (un)substituted C1-6 alkyl, (un)substituted CH2(C1-4 alkenyl), (un)substituted CH2(C1-6 alkynyl); X = anion of pharmaceutically acceptable acid]. Preparation of selected compds., e.g. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide, is included.

IT 518360-93-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quaternary ammonium compds. for treatment of irritable bowel syndrome)

RN 518360-93-5 CAPLUS

CN Benzenepropanaminium, 5-(hydroxymethyl)-N-methyl-N,N-bis(1-methylethyl)-2-(2-methyl-1-oxopropoxy)-γ-phenyl-, bromide, (γR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



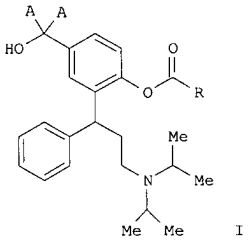
● Br^-

L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:878361 CAPLUS
DOCUMENT NUMBER: 141:370546
TITLE: Highly pure bases of 3,3-diphenyl propylamine monoesters for use in transdermal delivery systems
INVENTOR(S): Breitenbach, Armin; Meese, Claus; Wolff, Hans-Michael; Drews, Roland
PATENT ASSIGNEE(S): Schwarz Pharma Ag, Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089872	A1	20041021	WO 2004-EP3567	20040403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315917	A1	20041118	DE 2003-10315917	20030408
AU 2004228163	A1	20041021	AU 2004-228163	20040403
CA 2505848	A1	20041021	CA 2004-2505848	20040403
BR 2004006221	A	20050809	BR 2004-6221	20040403
EP 1613584	A1	20060111	EP 2004-725610	20040403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1802345	A	20060712	CN 2004-80009224	20040403
JP 2006522758	T	20061005	JP 2006-504989	20040403
US 2006014832	A1	20060119	US 2005-532836	20050426
NO 2005005078	A	20051031	NO 2005-5078	20051031

PRIORITY APPLN. INFO.:
DE 2003-10315917 A 20030408
WO 2004-EP3567 W 20040403

OTHER SOURCE(S): MARPAT 141:370546
GI



I

AB The invention relates to a compound of general formula (I) wherein A represents deuterium or hydrogen, R represents a group selected from C1-6 alkyl, C3-10 cycloalkyl or Ph, which can be substituted by C1-3 alkoxy, fluorine, chlorine, bromine, iodine, nitro, amino, hydroxyl, oxo, mercapto or deuterium. The C atom marked with a * (star) can be present in an (R) configuration, in an (S)-configuration or a mixture thereof. The invention

OVER
ODP 10/532836

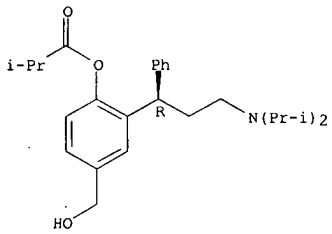
is characterized in that the above-mentioned compds. are free bases with a degree of purity of more than 97 wt %. The invention also relates to a method for the production of highly pure compds. of general formula (I) and to the use thereof in the production of medicaments. Thus (R)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol was reacted with isobutyric acid chloride to form fesoterodine. Fesoterodine was purified via the formation of its fumaric acid salt. 1.5 G of the highly pure fesoterodine was mixed with 8.5 g silicone adhesive Bio-PSA 7-4300 and applied to a foil in order to prepare a transdermal delivery system.

IT 286930-02-7P, Fesoterodine
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(highly pure bases of 3,3-di-Ph propylamine monoesters for use in transdermal delivery systems)

RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 777075-72-6P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(highly pure bases of 3,3-di-Ph propylamine monoesters for use in transdermal delivery systems)

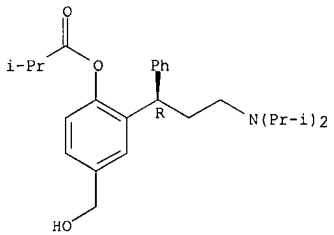
RN 777075-72-6 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, carbonate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 286930-02-7
CMF C26 H37 N O3

Absolute stereochemistry. Rotation (+).



CM 2

CRN 463-79-6
CMF C H2 O3

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:878163 CAPLUS
DOCUMENT NUMBER: 141:360690
TITLE: Combination therapies of asthma, COPD, allergic and infectious rhinitis
INVENTOR(S): Richards, Ivan Michael; Manning, Robert Everett
PATENT ASSIGNEE(S): Pfizer Inc, USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004209916	A1	20041021	US 2004-824315	20040413
CA 2522666	A1	20041028	CA 2004-2522666	20040405
WO 2004091596	A2	20041028	WO 2004-IB1170	20040405
WO 2004091596	A3	20050407		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1620083	A2	20060201	EP 2004-725755	20040405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

BR 2004009492	A	20060502	BR 2004-9492		20040405
JP 2006523674	T	20061019	JP 2006-506483		20040405
PRIORITY APPLN. INFO.:			US 2003-463975P	P	20030418
			WO 2004-IB1170	W	20040405

OTHER SOURCE(S): MARPAT 141:360690

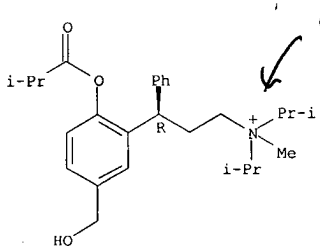
AB The invention is directed to methods of treating asthma, COPD, allergic rhinitis, and infectious rhinitis by administering a first pharmaceutical agent including one or more compds. selected from the quaternary ammonium compds. (Markush structures are included) and a second pharmaceutical agent including one or more pharmaceutical agents selected from Adenosine A2a Receptor Agonists, D2-Dopamine Receptor Agonists, Phosphodiesterase Inhibitors (PDE's), corticosteroids, norepinephrine reuptake inhibitors, 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulfonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3H)-one, and pharmaceutically acceptable salts thereof, and non-quaternized antimuscarinic compds.

IT 518360-93-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapies of asthma, COPD, allergic and infectious rhinitis)

RN 518360-93-5 CAPLUS

CN Benzenepropanaminium, 5-(hydroxymethyl)-N-methyl-N,N-bis(1-methylethyl)-2-(2-methyl-1-oxopropoxy)-γ-phenyl-, bromide, (γR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



QUATERNARY
NO GOOD

● Br^-

L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:875348 CAPLUS
DOCUMENT NUMBER:	142:147630
TITLE:	Fesoterodine, an advanced antimuscarinic for the treatment of overactive bladder: a safety update
AUTHOR(S):	Cole, Patrick
CORPORATE SOURCE:	Medical Information Dept., Prous Science, Barcelona, 08080, Spain
SOURCE:	Drugs of the Future (2004), 29(7), 715-720 CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER:	Prous Science
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

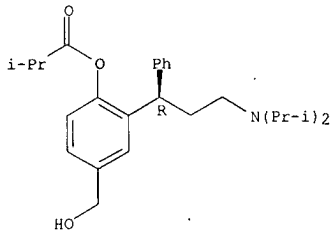
AB A review. The pillars of pharmacotherapy for overactive bladder (OAB) are antimuscarinic agents which inhibit bladder smooth muscle contractions through interference with acetylcholine action on muscarinic receptors of the detrusor smooth muscle. Despite the availability of different antimuscarinic compds., physicians and patients remain dissatisfied with current treatments due to adverse events and/or insufficient efficacy. Therefore, new agents with improved safety and efficacy profiles are needed for a more effective treatment of overactive bladder. Fesoterodine is a novel bladder-selective muscarinic antagonist that has shown potent antimuscarinic activity in vitro and in vivo. In multiple investigations, the agent has been shown to be safe and well tolerated in subjects of different ethnic origin, age and gender; in poor and extensive CYP2D6 metabolizers; in subjects taking concomitant medication inhibiting CYP3A4; in fed or fasted states; and in those suffering from hepatic impairment. No clin. relevant changes in heart rate, blood pressure, ECG parameters or laboratory analyses have been seen with therapeutic doses of fesoterodine in these studies. Furthermore, in a phase II clin. trial in patients with OAB, fesoterodine demonstrated rapid and significant efficacy on a variety of endpoints. The results of this trial encouraged the manufacturer (SCHWARZ PHARMA) to initiate a phase III clin. trial program for fesoterodine.

IT 286930-02-7, Fesoterodine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(advanced antimuscarinic fesoterodine for treatment of overactive bladder)

RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:872676 CAPLUS
DOCUMENT NUMBER:	141:337790
TITLE:	Transdermal administration of (R)-3,3-diphenylpropylamine monoesters
INVENTOR(S):	Breitenbach, Armin; Meese, Claus; Wolff, Hans-Michael; Drews, Roland
PATENT ASSIGNEE(S):	Schwarz Pharma Ag, Germany
SOURCE:	PCT Int. Appl., 68 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

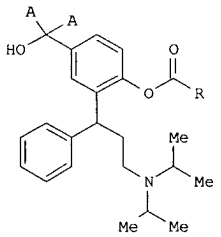
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089346	A1	20041021	WO 2004-EP3574	20040403

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10315878	A1	20041104	DE 2003-10315878	20030408
AU 2004228927	A1	20041021	AU 2004-228927	20040403
CA 2505780	A1	20041021	CA 2004-2505780	20040403
EP 1530461	A1	20050518	EP 2004-725614	20040403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004006212	A	20050816	BR 2004-6212	20040403
CN 1767820	A	20060503	CN 2004-80009176	20040403
JP 2006522759	T	20061005	JP 2006-504992	20040403
ZA 2005002681	A	20051013	ZA 2005-2681	20050401
US 2006029673	A1	20060209	US 2005-533683	20050426
NO 2005004644	A	20051010	NO 2005-4644	20051010
PRIORITY APPLN. INFO.:			DE 2003-10315878 A	20030408
			WO 2004-EP3574 W	20040403

OTHER SOURCE(S): MARPAT 141:337790
GI



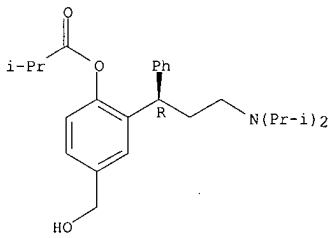
I

ODP OVER 10/533683

AB The invention relates to a device for transdermally administering a compound of formula (I), wherein A represents hydrogen or deuterium, R represents a group selected among C1-6 alkyl, C3-10 cycloalkyl, or Ph, each of which can be substituted by C1-3 alkoxy, fluoride, chlorine, bromine, iodine, nitro, amino, hydroxy, oxo, mercapto, or deuterium, the C atom marked by * (asterisk) being provided in the R configuration. The invention is characterized in that the compound of general formula (I) is provided in a polymer matrix and is released at a dose of 0.5 to 20 mg per day through human skin. The invention further relates to the use of said compds. of formula (I) for producing transdermal medicaments. Thus a silicone-based transdermal system was prepared by the hot-melt process. 8.5 G of an adhesive mixture composed of BIO-PSA 7-4300 from Dow-Corning and 5 weight/weight% ozokerite or ceresin was heated to 150°C for 20 min until a homogeneous melt was formed. 1.5 G fesoterodine were added to the melt; the mixture was kept for addnl. 5 min at 150°C; followed by application onto a preheated foil. 5 Cm2 samples were used for dissoln. studies.

IT 286930-02-7P, Fesoterodine
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(transdermal administration of (R)-3,3-diphenylpropylamine monoesters)
RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

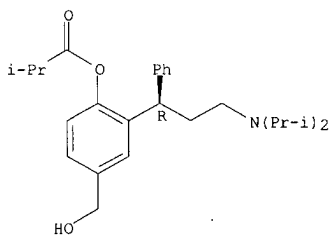
L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:761399 CAPLUS
DOCUMENT NUMBER:	141:254396
TITLE:	Fesoterodine a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome: results of a phase 2 controlled study
CORPORATE SOURCE:	Chapple C1, Royal Hallamshire Hospital, UK
SOURCE:	Neurourology and Urodynamics (2004), 23(5/6), 598-599 CODEN: NEUREM; ISSN: 0733-2467
PUBLISHER:	Wiley-Liss, Inc.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Fesoterodine as new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome is studied here.

IT 286930-02-7, Fesoterodine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimuscarinic fesoterodine for treatment of urgency-frequency syndrome)
RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

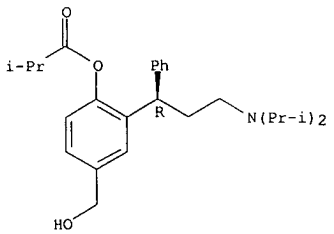


L4 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:993805 CAPLUS
DOCUMENT NUMBER: 140:331551
TITLE: Fesoterodine: Treatment of urinary incontinence muscarinic M3 antagonist
AUTHOR(S): Sorbera, L. A.; Castaner, J.; Lesson, P. A.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2003), 28(7), 647-651
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Urinary incontinence and overactive bladder are extremely common disorders affecting up to 12 and 20 million adults in the U.S., resp. Current pharmacotherapy includes peripherally acting compds. which modulate bladder smooth muscle contraction or centrally acting agents which modulate the neurol. control of urination. Anticholinergic agents inhibit bladder smooth muscle contraction through interference with acetylcholine action on muscarinic receptors on detrusor smooth muscle. However, the first anticholinergic agents were associated with a high rate of adverse events due to nonselectivity and targeting of several muscarinic subtypes and thus other organs. The search for novel, more bladder-selective antimuscarinic agents with better tolerability was initiated. Fesoterodine is a novel selective muscarinic M3 receptor antagonist that has shown potent antimuscarinic activity in vitro and in vivo and has been selected for further development as a treatment for urinary incontinence and overactive bladder.

IT 286930-02-7, Fesoterodine
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fesoterodine treatment of urinary incontinence as muscarinic M3 antagonist)
RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:950829 CAPLUS
DOCUMENT NUMBER: 140:13084
TITLE: Combination of selected opioids with other active substances for use in the therapy of urinary incontinence
INVENTOR(S): Christoph, Thomas
PATENT ASSIGNEE(S): Grunenthal G.m.b.H., Germany
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

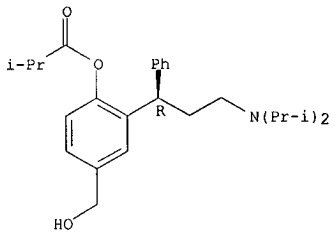
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099268	A1	20031204	WO 2003-EP5529	20030527
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10224107	A1	20031211	DE 2002-10224107	20020529
AU 2003240717	A1	20031212	AU 2003-240717	20030527
EP 1507520	A1	20050223	EP 2003-730120	20030527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005137194	A1	20050623	US 2004-998164	20041129
US 2006168942	A1	20060803	US 2005-545901	20050817
PRIORITY APPLN. INFO.:			DE 2002-10224107 A	20020529
			WO 2003-EP5529 W	20030527

OTHER SOURCE(S): MARPAT 140:13084

AB The invention discloses the use of a combination of opioids (e.g. tramadol) with other active substances for producing a drug for the treatment of urinary urgency or urinary incontinence. The invention also relates to corresponding medicaments and to a method for treating urinary urgency or urinary incontinence.

IT 286930-02-7, Fesoterodine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid combination with other active substances for treatment of urinary incontinence)
RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



DIFF. ASSIGNEE,
NO ODP
REJECTION
(NOT PRIOR ART EITHER)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:335062 CAPLUS
DOCUMENT NUMBER: 138:353732
TITLE: Quaternary ammonium compounds and their use as antimuscarinic agents
INVENTOR(S): Richards, Ivan; Cammarata, Sue K.; Wegner, Craig D.; Hawley, Michael; Warchol, Mark P.; Kontny, Mark; Morozowich, Walter; Kolbasa, Karen P.; Moon, Malcolm W.; Bonafoux, Dominique; Wolfson, Sergey G.; Lennon, Patrick J.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035599	A1	20030501	WO 2002-US34529	20021025
W: 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				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2464223	A1	20030501	CA 2002-2464223	20021025
US 2003158176	A1	20030821	US 2002-280906	20021025
US 6890920	B2	20050510		
BR 2002006207	A	20031223	BR 2002-6207	20021025
EP 1461306	A1	20040929	EP 2002-793840	20021025
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005524605	T	20050818	JP 2003-538115	20021025
NO 2003002938	A	20030825	NO 2003-2938	20030626
US 2005148672	A1	20050707	US 2005-74914	20050308
PRIORITY APPLN. INFO.:			US 2001-348930P P	20011026
			US 2002-361979P P	20020306
			US 2002-391521P P	20020625
			US 2002-280906 A1	20021025
			WO 2002-US34529 W	20021025

OTHER SOURCE(S): MARPAT 138:353732
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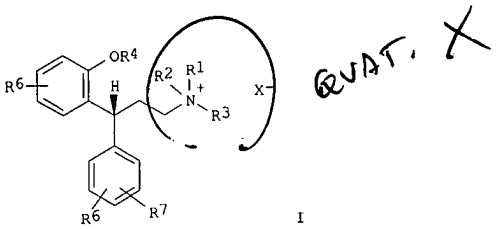


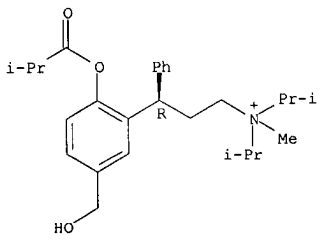
I

AB Novel quaternary ammonium compds. I [R1-R3 = (un)substituted alkyl; NR1R2, NR2R3, NR1R3 = heterocyclic; R4 = H, Me, acyl, alkoxycarbonyl, (un)substituted NH2; R5-R7 = H, OMe, OH, CONH2, SO2NH2, F, Cl, Br, I, CF3, (un)substituted alkyl; X = anion of a pharmaceutically acceptable acid] were prepared for use as antimuscarinic agents. Thus, tolterodine tartrate was converted to the free base and quaternized with MeI to give (R)-5,2-Me(OH)C6H3CHPhCH2CH2N+(CHMe2)2Me I- which has high affinity, but little selectivity for M1-M5 muscarinic receptors.

IT 518360-93-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn.of diarylpropylammonium salts as antimuscarinic agents)

RN 518360-93-5 CAPLUS
CN Benzenepropanaminium, 5-(hydroxymethyl)-N-methyl-N,N-bis(1-methylethyl)-2-(2-methyl-1-oxopropoxy)-γ-phenyl-, bromide, (γR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br-

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:449738 CAPLUS
DOCUMENT NUMBER: 135:61141
TITLE: Preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters.
INVENTOR(S): Meese, Claus
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19955190	A1	20010621	DE 1999-19955190	19991116
DE 29923134	U1	20000803	DE 1999-29923134	19991116
CA 2389749	A1	20010525	CA 2000-2389749	20001115
WO 2001035957	A2	20010525	WO 2000-EP11309	20001115
WO 2001035957	A8	20010621		
WO 2001035957	A3	20011227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,				

YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 200126667	A	20010530	AU 2001-26667		20001115
AU 778132	B2	20041118			
BR 2000015610	A	20020730	BR 2000-15610		20001115
EP 1230209	A2	20020814	EP 2000-989857		20001115
EP 1230209	B1	20050112			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
HU 200204034	A2	20030328	HU 2002-4034		20001115
JP 2003514018	T	20030415	JP 2001-537950		20001115
NZ 519230	A	20041126	NZ 2000-519230		20001115
EP 1481964	A1	20041201	EP 2004-18487		20001115
EP 1481964	B1	20060823			
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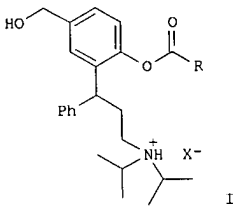
AT 286872	T	20050115	AT 2000-989857		20001115
PT 1230209	T	20050531	PT 2000-989857		20001115
ES 2236032	T3	20050716	ES 2000-989857		20001115
EP 1690536	A2	20060816	EP 2006-11207		20001115
EP 1690536	A3	20060823			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
AT 337293	T	20060915	AT 2004-18487		20001115
ZA 2002003315	A	20030725	ZA 2002-3315		20020425
US 6858650	B1	20050222	US 2002-130214		20020514
NO 2002002314	A	20020515	NO 2002-2314		20020515
HK 1045148	A1	20050506	HK 2002-106545		20020905
HK 1067114	A1	20061020	HK 2004-110231		20020905
NO 2006005380	A	20020515	NO 2006-5380		20061122

PRIORITY APPLN. INFO.:

DE 1999-19955190	IA	19991116
EP 2000-989857	A3	20001115
EP 2004-18487	A3	20001115
WO 2000-EP11309	W	20001115
HK 2002-106545	A	20020905

OTHER SOURCE(S): MARPAT 135:61141

GI



I

ODP. OVER
US 6858650

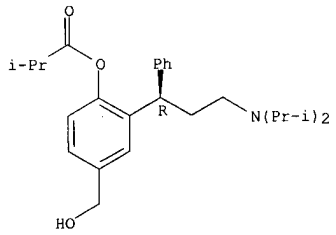
AB Title compds. [I; R = alkyl, cycloalkyl, (substituted) Ph; X- = residue of a physiol. acceptable (in)organic acid], were prepared Thus, (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate (II) (preparation given) in 2-butanone was treated with fumaric acid under warming to give 83.1% II.hydrogen fumarate.

IT 286930-02-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)

RN 286930-02-7 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 286930-03-8P 345663-07-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)

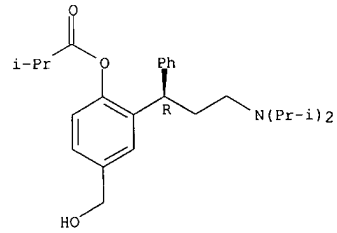
RN 286930-03-8 CAPLUS

CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 286930-02-7
CMF C26 H37 N O3

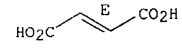
Absolute stereochemistry. Rotation (+).



CM 2

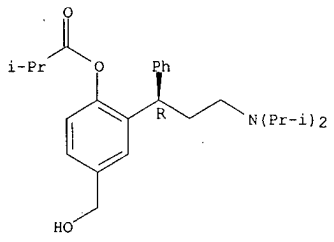
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



RN 345663-07-2 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

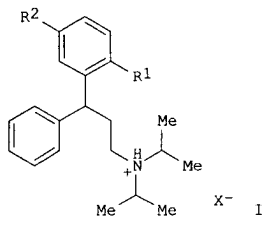


● HCl

L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:533448 CAPLUS
DOCUMENT NUMBER: 133:155419
TITLE: Stable salts of novel derivatives of 3,3-diphenylpropylamines
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Gebrauchsmusterschrift, 37 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 29923134	U1	20000803	DE 1999-29923134	19991116
DE 19955190	A1	20010621	DE 1999-19955190	19991116
PRIORITY APPLN. INFO.:			DE 1999-19955190	IA 19991116

OTHER SOURCE(S): MARPAT 133:155419
GI



I

AB 3,3-Diphenylpropylamine salts I [R1 = RCO2; R = C1-6 alkyl, C3-10 cycloalkyl, (substituted) Ph; R2 = CH2OH; X = inorg. or organic acid] are prepared for use as prodrugs of agents for treatment of urinary incontinence and other spasmogenic disorders. I show improved absorption through biol. membranes and improved metabolic patterns and are easily crystallized I are prepared from I free base (R1 = PhCH2O, R2 = CO2Me) by debenzylation, reduction, acylation, and combination with HX. Thus, R-(-)-I-HCl (R1 = PhCH2O, R2 = CO2H) was esterified by refluxing in acidic MeOH, the ester was reduced with LiAlH4, the resulting carbinol was reduced with Raney Ni/H2, and the product [R-(+)-I free base, R = CHMe2] was converted to its H fumarate salt by heating with equimolar fumaric acid in 2-butanone; the salt was crystallized by addition of cyclohexanone and cooling to 0°.

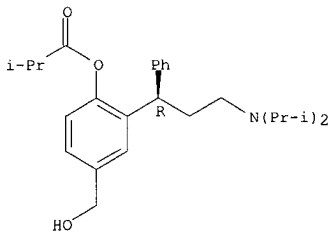
IT 286930-03-8P 286930-04-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stable salts of novel derivs. of diphenylpropylamines)

RN 286930-03-8 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 286930-02-7
CMF C26 H37 N O3

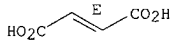
Absolute stereochemistry. Rotation (+).



CM 2

CRN 110-17-8
CMF C4 H4 O4

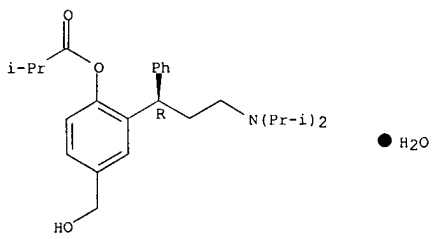
Double bond geometry as shown.



RN 286930-04-9 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, hydrochloride, monohydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

NO U.S. CASE 1
NOT PRIOR ART



● HCl

● H_2O

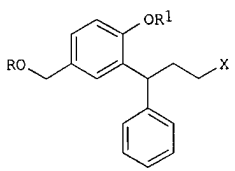
L4 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:736261 CAPLUS
DOCUMENT NUMBER: 131:336818
TITLE: Preparation of 3,3-diphenylpropylamines as antimuscarinic agents.
INVENTOR(S): Sparf, Bengt; Meese, Claus O.
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 957073	A1	19991117	EP 1998-108608	19980512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2328920	A1	19991118	CA 1999-2328920	19990511
WO 9958478	A1	19991118	WO 1999-EP3212	19990511
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941412	A	19991129	AU 1999-41412	19990511
AU 748057	B2	20020530		
BR 9910406	A	20010109	BR 1999-10406	19990511
EP 1077912	A1	20010228	EP 1999-924929	19990511
EP 1077912	B1	20020703		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 200100779	A2	20010828	HU 2001-779	19990511
TR 200003319	T2	20011221	TR 2000-200003319	19990511
AT 220056	T	20020715	AT 1999-924929	19990511
EP 1254890	A1	20021106	EP 2002-13481	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NZ 507487	A	20021126	NZ 1999-507487	19990511
PT 1077912	T	20021129	PT 1999-924929	19990511
ES 2181443	T3	20030216	ES 1999-924929	19990511
RU 2199525	C2	20030227	RU 2000-125813	19990511
JP 2003519079	T	20030617	JP 2000-548284	19990511
CN 1690041	A	20051102	CN 2005-10070299	19990511
CZ 296605	B6	20060412	CZ 2000-3774	19990511
ZA 2000005728	A	20010305	ZA 2000-5728	20001017
NO 2000005669	A	20010111	NO 2000-5669	20001110
US 6713464	B1	20040330	US 2001-700094	20010102
HK 1046269	A1	20050923	HK 2002-107859	20021030
US 2004186061	A1	20040923	US 2004-766263	20040127
US 2006270738	A1	20061130	US 2005-201756	20050810
JP 2007084552	A	20070405	JP 2006-283861	20061018

PRIORITY APPLN. INFO.:

EP 1998-108608	A	19980512
CN 1999-806038	A3	19990511
EP 1999-924929	A3	19990511
JP 2000-548284	A3	19990511
WO 1999-EP3212	W	19990511
US 2001-700094	A1	20010102
US 2004-766263	A1	20040127

OTHER SOURCE(S): MARPAT 131:336818
GI



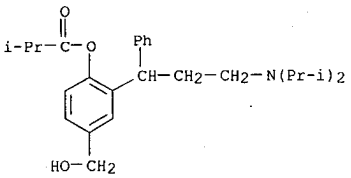
I

ODP OVER
10/766263

AB Title compds. (I; R = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, CHO, Ac, propionyl, isobutyryl, aminocarbonyl, aminosulfonyl, MeO2C, etc.; R1 = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, phenylalkyl; Z = NR8R9; R8, R9 = hydrocarbyl; NR8R9 = atoms to form a ring; with a proviso), were prepared as antimuscarinic agents (no data). Thus, 4-bromophenol, cinnamoyl chloride, and Et3N were stirred 18 h in CH2Cl2 to give 99.8% 3-phenylacrylic acid 4-bromophenyl ester. This was refluxed 2 h with HOAc/H2SO4 to give 43.8% 6-bromo-4-phenylchroman-2-one. The latter was refluxed with benzyl bromide, K2CO3, and NaI in acetone/MeOH to give 102.1% crude Me 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionate, which was stirred with LiAlH4 in THF to give 96.3% 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol. This was stirred with tosyl chloride and pyridine in CH2Cl2 for 18 h to give 93.6% tosylate ester, which was refluxed 97 h with diisopropylamine in MeCN to give 77.9% [3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]diisopropylamine. The latter was converted in several steps to 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, which was acylated to give I.

IT 250214-44-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3,3-diphenylpropylamines as antimuscarinic agents)

RN 250214-44-9 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> LOGHOLD
LOGHOLD IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> LOG HOLD

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	90.06	264.62
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-13.26	-13.26

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 09:33:43 ON 15 APR 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

26646 7590 04/20/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	11/201,756	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 28-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 28-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 10 August 2005 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/700,094.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10Aug05,13Nov06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Substitute Specification filed 14 July 2006 and the Preliminary Amendment filed 11 October 2005 have been entered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 20-23 of U.S. Patent No. 6,713,464. Although the conflicting claims are not identical, they are not patentably distinct from each other because in claim 4 of the patent, the compound according to instant claim 28 is named – R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester. Claim 4 of the patent depends from claim 2 of the patent,

which in turn depends ultimately from claim 1 therein. So, claims 1, 2 and 4 fully embrace the subject matter of instant claim 1.

The patent teaches that compounds according to the invention disclosed therein are also in the form of salts with physiologically acceptable acids (col. 4, lines 25-31), in a pharmaceutical composition (col. 24, lines 16-36). A pharmaceutical composition of compounds according to the invention disclosed in the patent is specified in claim 20 thereof. Thus, the salts of compounds according to the invention disclosed in US 6,713,464 are contemplated as being components of a pharmaceutical composition and therefore instant claims 29 and 30, drawn to a salt of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, with a physiologically acceptable acid, and a pharmaceutical composition comprised thereof, are rendered obvious by the claims of US 6,713,464, particularly claim 20.

Instant claims 31-34 are rendered obvious by claims 21-24 of US 6,713,464, because the compound according to instant claim 29 is within the scope of claim 1 of the patent (and is specifically claimed in claim 4 of the patent), and claims 21-24 of the patent depend ultimately from claim 1 thereof. Claims 21-24 of the patent correspond in language and format to instant claims 31-34.

Those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent [*In re* Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)]. So, the specification of US 6,713,464 was relied upon in making the determination that a salt of a compound according to the claims of the patent, with a physiologically acceptable acid, is

contemplated by the claims of the patent, even though no salt of any of the compounds is explicitly recited in those claims. One of ordinary skill in the art of pharmacy would clearly find it obvious, in light of the disclosure of the invention, to incorporate a salt of a compound according to claim 1, 2 or 4 of the patent into a pharmaceutical composition comprised of one of those compounds.

Claims 28-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5 and 21-24 of U.S. Patent No. 6,858,650. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound named in instant claim 28 is named in claim 5 of the patent, in salt form with a physiologically acceptable acid. Claim 5 of the patent depend from claim 3 therein, which in turn depends ultimately from claim 1. Thus, claims 1 and 3 include the subject matter of instant claim 28 as well as claim 5 of that patent does.

Instant claims 31-34 correspond in language and form with claims 21-24 of the patent. Since the compound according to instant claim 28 is named in the claims of the patent, and is included in the broader generic claim 1 of the patent, the method-of-treatment claims 21-24 of the patent embrace the corresponding claims 31-34 of the instant application.

Claims 28 and 30-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 39, 49 and 63-65 of copending Application No. 10/532,836. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the compound named in instant claim 28 is also named in claim 39 of the copending application. Because claim 39 of the copending application depends from claim 35 thereof, claim 35 includes the subject matter of instant claim 28 as well. A pharmaceutical composition comprising a compound according to claim 35 of the copending application is claimed in claim 49 thereof, and that claim (claim 49) corresponds to instant claim 30, drawn to a pharmaceutical composition comprising a compound according to instant claim 28.

Claims 63-65 of the copending application are drawn to a method of treating urinary incontinence by administering a compound according to claim 35 thereof, to a human. Since claim 35 of the copending application includes the subject matter of instant claim 28, the method-of-treatment claims wherein a compound according to claim 35 is administered includes the subject matter of the corresponding method-of-treatment claims in the instant application, claims 31-34,

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 28-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 30 of copending Application No. 10/533,683. Although the conflicting claims are not identical, they are not patentably distinct from each other because a compound according to instant claim 28, in salt form with a physiologically acceptable acid is disclosed in the specification (page 14, lines 20-23) of the copending application, and is taught to be the especially preferred compound according to Formula I contained in the device according to claim 1 of that

application. Thus, subject matter of instant claims 28-30 is embraced in claim 1 of the copending application, when interpreted in light of the specification of that application. Claim 30 of the copending application is drawn to the treatment of incontinence comprising the administration of a device according to claim 1of that application. Thus, subject matter of instant claims 31-34 is embraced in claim 30 of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Specification

The specification is objected to under 37 C.F.R. 1.77(b), for not setting out the proper sections in the following order:

Background of the invention,

Brief summary of the invention,

Brief description of the drawings,

Detailed description of the invention.

Appropriate correction is required.

The specification is also objected to under 37 C.F.R. 1.78(a)(5)(iii), for not including the continuity data, referencing the fact that the instant application is a continuation of application serial number 10/766,263, now allowed, which is a continuation of application serial number 09/700,094, now U.S. Patent Number 6,713,464.

Appropriate correction is required.

Allowable Subject Matter

If the obviousness-type double patenting rejections set forth in this Office action are overcome, by the filing of appropriate Terminal Disclaimers, and the objection to the specification is attended to by correcting the indicated deficiencies, claims 28-34 will be allowable.

Closest prior art is US 5,686,464 (Johansson et al).

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 9:00am to 5:00pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

ZACHARY C. TUCKER
PRIMARY EXAMINER

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449	ATTY. DOCKET NO. 12961/46103	APPLICATION NO. 11/201,756
	APPLICANT Claus MEESE, et al.	
	FILING DATE August 10, 2005	GROUP 1624

U. S. PATENT DOCUMENTS*

EXAMINER INITIAL	PATENT/PUBLICATION NUMBER	PATENT/PUBLICATION DATE	NAME	CLASS	SUBCLASS	FILING DATE
ZT	2,556,636	June 12, 1951	Nathan Sperber et al.			
ZT	2,567,245	September 11, 1951	Nathan Sperber et al.			
ZT	2,676,964	April 27, 1954	Nathan Sperber et al.			
ZT	3,261,841	July 19, 1966	Bernard L. Zenitz			
ZT	3,446,901	May 27, 1969	G. J. Macclesfield			
ZT	4,988,730	January 29, 1991	Korbonits et al.			
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ZT	6,517,864	February 11, 2003	Orup Jacobsen et al.			
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ZT	6,630,162	October 7, 2003	Nilvebrant et al.			
ZT	6,689,916	February 10, 2004	Andersson et al.			
ZT	6,713,464	March 30, 2004	Meese et al.			
ZT	6,770,295	August 3, 2004	Kreilgard et al.			
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ZT	6,809,214	October 26, 2004	Meese			
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ZT	6,858,650	February 22, 2005	Meese			
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ZT	2003/0158176	August 21, 2003	Richards et al.			
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*- copies of U.S. references are not enclosed

EXAMINER [signature] DATE 14 APRIL 2007

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ZT	925 468 (in German, with English translation)	March 21, 1955	DE			YES	
ZT	1 216 318 (in German, with English translation)	May 12, 1966	DE			YES	
ZT	325 571	July 26, 1989	EP				
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* ZT	WO 99/58478	November 18, 1999	PCT				
ZT	WO 00/12069	March 09, 2000	PCT				
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EXAMINER _____ DATE 14 APRIL 2007

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
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ZT	WO 04/019892	March 11, 2004	PCT				

*- English translation of claims provided
**- English translation of abstract provided

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EXAMINER	DATE CONSIDERED
	14 APRIL 2007

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.

IDS 8/10/05

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	ATTY. DOCKET NO. 12961/46102	APPLICATION NO. [redacted] 11/201,756
	APPLICANT Claus MEESE et al.	
	FILING DATE August 10, 2005	GROUP 1624

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	PATENT NUMBER	PATENT DATE	NAME	CLASS	SUBCLASS	FILING DATE*
ZT	6,313,132	November 06, 2001	R. Johansson et al.			
ZT	~~5,688,464~~ 5,686,464	November 11, 1997	R. Johansson et al.			

*- if relevant

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EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
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EXAMINER	DATE CONSIDERED
	19 APRIL 2007

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.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
EAST	**USPG-PUB**	**4/15/2007**	**ZT**
514/551, 560/140 CROSS REFERENCED WITH TEXT TERMS		AS SHOWN ON THE ATTACHED SEARCH HISTORY	

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
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PALM - INVENTORS' NAMES SEARCHED.	4/15/2007	ZT
EAST - USPAT, USPG-PUB, EPO, JPO, DERWENT, FPRS		
CLASS/SUBCLASSES 514/551, 560/140 CROSS-REFERENCED WITH TEXT TERMS: ["DIPHENYLPROPYLAMINES" or "TOLTERODINE"]	4/15/2007	ZT
STN - STRUCTURE SEARCH PERFORMED IN "REGISTRY" FILE, ANSWER SET CROSS-REFERENCED INTO "CAPLUS" FILE TRANSCRIPT ATTACHED	4/15/2007	ZT

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
11/201,756	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date
Final	Original	4/2007
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Bib Data Sheet

CONFIRMATION NO. 3812

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/201,756	08/10/2005 RULE	514	1624	12961/46103

APPLICANTS

Claus Meese, Monheim, GERMANY;
Bengt Sparf, Trangsund, SWEDEN;

**** CONTINUING DATA ****************************** ALLOWED 7/17/06

This application is a CON of 10/766,263 01/27/2004 which is a CON of 09/700,094 01/02/2001 PAT 6,713,464
which is a 371 of PCT/EP99/03212 05/11/1999

**** FOREIGN APPLICATIONS *********************

EUROPEAN PATENT OFFICE (EPO) 98108608.5 05/12/1998

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 02/23/2006

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☒ yes ☐ no	GERMANY	1	7	4
35 USC 119 (a-d) conditions met: ☒ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged: Examiner's Signature / Initials ET				

ADDRESS
26646

TITLE

Novel derivatives of 3,3-diphenylpropylamines

FILING FEE RECEIVED	FEES: Authority has been given in Paper
1580	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

- ☐ All Fees
- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
- ☐ Other _____
- ☐ Credit

Docket No.: 12961/46103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Meese et al.
SERIAL NO.	:	11/201,756
FILED	:	August 10, 2005
FOR	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
EXAMINER:		Tucker
GROUP ART UNIT	:	1624

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
Date: October 23, 2007
Signature: Chandra Seanard

AMENDMENT

SIR:

In response to the Office Action dated April 20, 2007, please consider the following amendments and remarks. Enclosed herewith are a Petition for the Extension of Time and four Terminal Disclaimers.

10/25/2007 CCHAU1 00000018 110600 11201756
01 FC:1253 1050.00 DA

IN THE SPECIFICATION

At page 1, after the title, of the Substitute Specification filed July 10, 2006, please amend the specification by inserting the following:

> This application is a continuation of U.S. Patent Application Serial No. 10/766,263, filed January 27, 2004, now U.S. Patent No. 7,230,030, which is a continuation of U.S. Patent Application Serial No. 09/700,094, filed January 2, 2001, now U.S. Patent No. 6,713,464, which is a 371 of PCT/EP99/03212, filed May 11, 1999.

At page 1, before the paragraph beginning "In man, normal urinary bladder contractions ...," of the Substitute Specification filed July 10, 2006, please amend the specification by inserting the following:

Background of the Invention

At page 3, before the paragraph beginning "It is an object of the present invention ...," of the Substitute Specification filed July 10, 2006, please amend the specification by inserting the following:

Brief Summary of the Invention

At page 8, before the paragraph beginning "In the compounds according to the present invention, the term "alkyl" preferably ...," of the Substitute Specification filed July 10, 2006, please amend the specification by inserting the following:

Detailed Description of the Invention

Remarks

Claims 28-34 are pending.

The double patenting rejections

Claims 28-34 were rejected for obviousness-type double patenting over claims 1, 2, 4, and 20-23 of U.S. Patent No. 6,713,464.

Enclosed herewith is a Terminal Disclaimer over U.S. Patent No. 6,713,464. In view of the this Terminal Disclaimer, it is respectfully requested that this rejection be withdrawn.

Claims 28-34 were rejected for obviousness-type double patenting over claims 1, 3, 5, and 21-24 of U.S. Patent No. 6,858,650.

Enclosed herewith is a Terminal Disclaimer over U.S. Patent No. 6,858,650. In view of the this Terminal Disclaimer, it is respectfully requested that this rejection be withdrawn.

Claims 28, and 30-34 were rejected for obviousness-type double patenting over claims 35, 39, 49, and 63-65 of U.S. Patent Application Serial No. 10/532,836.

Enclosed herewith is a Terminal Disclaimer over U.S. Patent Application Serial No. 10/532,836. In view of the this Terminal Disclaimer, it is respectfully requested that this rejection be withdrawn.

Claims 28, and 30-34 were rejected for obviousness-type double patenting over claims 1 and 30 of U.S. Patent Application Serial No. 10/533,683.

Enclosed herewith is a Terminal Disclaimer over U.S. Patent Application Serial No. 10/533,683. In view of the this Terminal Disclaimer, it is respectfully requested that this rejection be withdrawn.

Objections to the specification

The specification was objected to for not setting out the proper sections in the proper order.

The specification has been amended to insert section headings. The Applicants note that the Substitute Specification filed July 10, 2006 already contained a "Brief Description of the Drawing" section heading on page 8.

The specification was objected to for not including the continuity data.

The specification has been amended to insert the continuity data.

In view of the above, it is respectfully requested that these objections be withdrawn.

The time for responding to the Office Action was set for July 20, 2007. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response. Please charge any corresponding fees for the Petition to Kenyon & Kenyon LLP's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing.

Respectfully submitted,

Date: October 22, 2007 BY: 

Joseph A. Coppola
Reg. No. 38,413

KENYON & KENYON
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

PTO/SB/26 (04-07)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 6,858,650 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

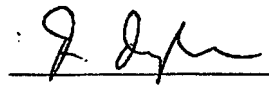
expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney or agent of record. Reg. No._____



Signature — 10/15/2007 Date

Dr.F.Dreßen
Senior Patent Counsel
Typed or printed name

10/25/2007 CCHAU1 00000018 110600 11201756
02 FC:1814 130.00 DA

+49 2173 481806
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT

Docket Number (Optional): 12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 6,713,464 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

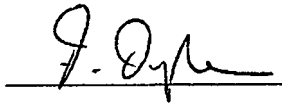
expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney or agent of record. Reg. No._____



Signature

10/15/2007
Date

Dr. F. Dreßen
Senior Patent Counsel
Typed or printed name

10/25/2007 CCHAU1 00000018 110600 11201756

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Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional): 12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 10/533,683, filed on April 26, 2005, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney or agent of record. Reg. No. _____

Signature	Date: 10/15/2007
Dr.F.Dreßen Senior Patent Counsel Typed or printed name	

10/25/2007 CCHAU1 00000018 110600 11201756

04 FC:1814 130.00 DA

+49 2173 481806
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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PTO/SB/25 (07-06)
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 10/532,836, filed on April 26, 2005, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. ☐ The undersigned is an attorney or agent of record. Reg. No. _____

	10/15/2007
Signature	Date
Dr.F.Dreßen	
Senior Patent Counsel	
Typed or printed name	
+49 2173 481806	
Telephone Number	

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DTJ

APPLICANT	:	Meese et al.
SERIAL NO.	:	11/201,756
FILED	:	August 10, 2005
FOR	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
EXAMINER	:	Tucker
GROUP ART UNIT	:	1624

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 as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Date: October 22, 2007

Signature: Theresa A.E. Doonan

TRANSMITTAL OF AMENDMENT, TERMINAL DISCLAIMERS AND EXTENSION OF TIME

S I R:

In response to the Office Action of April 20, 2007, Applicant submits herewith an Amendment in the above-identified application.

Applicant also submits four (4) Terminal Disclaimers to Obviate a Double Patenting Rejection Over a Prior Patent/Application for the following patents: 6,858,650; 6,713,464 and the following patent applications: 10/533,683; 10/532,836.

Applicant hereby requests a three-month extension of time for responding to this Office Action. The extended period for response expires on October 22, 2007 (as October 20, 2007 falls on a Saturday). The amount due with respect to the extension of time is calculated to be $1,050.00.

Please charge the $1,050.00 extension fee to Kenyon & Kenyon LLP Deposit Account No. **11-0600**

The Commissioner is also authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. **11-0600.** A copy of this form is enclosed for charging purposes.

Respectfully submitted,

KENYON & KENYON LLP

Dated: October 22, 2007 By: Joseph A. Coppola

Joseph A. Coppola
(Registration No. 38,413)

One Broadway
New York, New York 10004
(212) 425-7200
CUSTOMER NO. 26646

11/201,756

UPDATED

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	(514/551OR560/140).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2007/11/02 14:44
L2	0	(514/551OR560/140).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2007/11/02 14:44
L3	0	(514/551OR560/140).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2007/11/02 14:44
L4	345	514/551 OR 560/140	USPAT	OR	OFF	2007/11/02 14:44
L5	6	L4 AND (TOLTERODINE OR DIPHENYLPROPYLAMINE)	USPAT	OR	ON	2007/11/02 14:45

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 10/25/07	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

6713464 (Disapproved/agent not of record)

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 10/25/07	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

10/533683 (Disapproved/agent not of record)

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 10/25/07	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

6858650 (Disapproved/agent not of record)

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 10/25/07	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

10/532836 (Disapproved/agent not of record)

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UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

26646 7590 11/29/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/29/2007

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	02/29/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26646 7590 11/29/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

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Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	02/29/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-551000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____ 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

26646 7590 11/29/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/29/2007

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 156 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 156 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No. 11/201,756	Applicant(s) MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *25 October 2007*.

2. ☒ The allowed claim(s) is/are *28-34*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *09/700,094* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Response to Amendment

As requested by applicants in the correspondence filed 25 October 2007 (hereinafter "present amendment"), which is in reply to the Office action mailed 20 April 2007 (hereinafter "previous Office action"), the specification has been amended at pages 1, 3 and 8.

Terminal Disclaimers

The four Terminal Disclaimers which have been submitted 25 October 2007 have each been entered, recorded and are proper. The Terminal Disclaimers are over U.S. Patent Nos. 6,713,464 and 6858,560 and also over copending United States Patent Application Nos. 10/532,836 and 10/533,683.

Status of Double Patenting Rejections

In view of the Terminal Disclaimers filings noted immediately above, all Double Patenting rejections which were set out in the previous Office action are hereby withdrawn.

Status of Objections to the Specification

In the previous Office action, objection to the specification was made based on the lack of proper headings for each of the sections prescribed by 37 C.F.R. 1.77(b) and for lack of continuity data on page one of the specification which is prescribed by 37 C.F.R. 1.78(a)(5)(iii).

In view of the present amendment, which adds the missing elements of the specification, the objections are all hereby withdrawn.

Allowable Subject Matter

Claims 28-34 are now allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany

the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:
Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-872-9306, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

ZACHARY C. TUCKER
PRIMARY EXAMINER

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
ZT		Cole, "Fesoterodine, an advanced antimuscarinic for the treatment of overactive bladder: A safety update," 2004, Drugs of the Future 29:715-720
ZT		Committee for Proprietary Medicinal Products, "The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products," CPMP/986/96, December 17, 1997
ZT		Detrol® package insert, Pharmacia & Upjohn Co., April, 2004
ZT		Diokno et al., "Tolterodine (Detrol®) improves incontinence and nocturia in urological based study," 1999 April, J. Urol. 161 (4 Suppl):256, abstract 987
ZT		Ekstrom et al., "Effects of tolterodine on bladder function in healthy volunteers," Journal of Urology 153(Suppl.):394A, abstract 662 from the 19th Annual Meeting of the American Urological Association, Las Vegas, April 23-28, 1995
ZT		Gardner & Altman, "Confidence intervals rather than P values: estimation rather than hypothesis testing," 1986, Br. Med. J. 292:746-750
ZT		Gillberg et al., "Tolterodine, a new agent with tissue effect selectivity for urinary bladder," 1994, Neurourology and Urodynamics 13:435-436, abstract 60B from International Continence Society 24th Annual Meeting, Prague, Czech Republic, August 1994
ZT		Gillberg et al., "Comparison of the in vitro and in vivo profiles of tolterodine with those of subtype-selective muscarinic receptor antagonists," 1998, European Journal of Pharmacology 349: 285-292
ZT		Hills et al., "Tolterodine," 1998, Drugs 55:813-820
ZT		Jonas et al., "Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation," 1997, World J. Urol. 15:144-151
ZT		Kang et al., "Cardiac ion channel effects of Tolterodine," 2004, J. Pharmacol. Exper. Thera. 308:935-940
ZT		Kershen & Hsieh, "Preview of new drugs for overactive bladder and incontinence: darifenacin, solifenacin, trospium, and duloxetine," Curr. Urol. Rep. 5:359-367 (2004)
ZT		Klosa, "Eine Neue Synthesemethode der Darstellung von Diarylalkylaminen," 1966, Journal für Praktische Chemie 4:312-334 (in German) with English translation
ZT		Klosa, "Eine Neue Synthese von Diphenylisopropylaminen," 1966, Journal für Praktische Chemie 4:335-340 (in German, with English translation)
ZT		Larsson et al., "Tolterodine in the treatment of overactive bladder: analysis of the pooled phase II safety and efficacy data," 1999, Urology 53: 990-998
ZT		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
ZT		Millard et al., "Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity," 1999, J. Urol. 161:1551-1555
ZT		Modiri et al., "Effect of muscarinic antagonists on micturition pressure measured by cystometry in normal, conscious rats," 2002, Urology 59:963-968
ZT		Naerger et al., "Effect of tolterodine on electrically induced contractions of isolated human detrusor muscle from stable and unstable bladders," 1995, Neurourology and Urodynamics 14:524-526, abstract 76 from International Continence Society 25th Annual Meeting, Sydney, Australia, October 1995
ZT		Netzer, et al., "Screening lead compounds for QT interval prolongation" Drug Discovery Today Vol. 6, No. 2, pp.78-84, January 2001
ZT		Nilsson et al., "Comparison of a 10 mg controlled release oxybutynin tablet with a 5 mg oxybutynin tablet in urge incontinence patients," 1997, Neurourol. Urodyn. 16:533-542
ZT		Nilvebrant & Sparf, "Receptor binding profiles of some selective muscarinic antagonists," 1988, European Journal of Pharmacology 151:83-96
ZT		Nilvebrant & Sparf, "Differences between Binding Affinities of some Antimuscarinic Drugs in the parotid Gland and those in the Urinary Bladder and Ileum" Acta Pharmacol. et toxicol. Vol. 53, No. 4, pp. 304-313, October 1983

EXAMINER [signature] Page 4 DATE 14 APRIL 2007

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
ZT		Nilvebrant et al., "The in vitro pharmacological profile of tolterodine – a new agent for the treatment of urinary urge incontinence," 1994, Neurourology and Urodynamics 13:433-435, abstract 60A from International Continence Society 24th Annual Meeting, Prague, Czech Republic, August 1994
ZT		Nilvebrant et al., "Tolterodine is not subtype (m1-m5) selective but exhibits functional bladder selectivity in vivo," 1996, Neurourology and Urodynamics 15:310-311, abstract 34 from the 26th Annual Meeting of the International Continence Society, Athens, Greece, August 27-30, 1996
ZT		Nilvebrant, "Tolterodine and terodiline – different pharmacological profiles," pages 141-142, abstract 181a, from the 27th Annual meeting of the International Continence Society, Yokohama, Japan, September 1997
ZT		Nilvebrant et al "Tissue distribution of tolterodine and its metabolites: low penetration into the central nervous system," 2000, European Urology 37(Suppl. 2):84, abstract 333 from the XVth Congress of the European Association of Urology, Brussels, Belgium, April 12-15, 2000
ZT		Nilvebrant, "The mechanism of action of tolterodine," 2000, Reviews in Contemporary Pharmacotherapy 11:13-27
ZT		Olsson et al., "Food increases the bioavailability of tolterodine but not effective exposure," 2001, J. Clin. Pharmacol. 41:298-304
ZT		Olsson & Szamosi, "Food does not influence the pharmacokinetics of a new extended release formulation of tolterodine for once daily treatment of patients with overactive bladder," 2001, Clinical Pharmacokinetics 40:135-143
ZT		Olsson & Szamosi, "Multiple dose pharmacokinetics of a new once daily extended release formulation versus immediate release tolterodine," 2001, Clinical Pharmacokinetics 40:227-235
ZT		Pharmacology/Toxicology Review from Application Number 21-518, Center for Drug Evaluation and Research, pp. 1-3. (2001)
ZT		Rentzhog et al., "Efficacy and safety of tolterodine in patients with detrusor instability: a dose ranging study," 1998, Br. J. Urol. 81:42-48
ZT		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
ZT		Sachse et al., "Pharmacodynamics of multiple dose treatment with the novel antimuscarinic drug fesoterodine," 2002, Nauyn-Schmiedeberg's Arch. Pharmacol. 365 (Suppl. 1):413
ZT		Sachse et al., "Safety and pharmacokinetics of the novel bladder-selective antimuscarinic drug fesoterodine in populations of different age or gender," 2002, Proceedings of the International Continence Society, 32:441
ZT		Sachse et al., "Safety and pharmacokinetics of the novel bladder-selective antimuscarinic fesoterodine in populations of different ethnic origin," 2003, Proceedings of the International Continence Society, 33:377
ZT		Sachse et al., "Dose-proportional pharmacokinetics of the new antimuscarinic fesoterodine," 2003, Nauyn-Schmiedeberg's Arch. Pharmacol. 367 (Suppl. 1):446
ZT		Sachse et al., "Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel, bladder-selective antimuscarinic fesoterodine," 2003, Eur. Urol. Suppl 2:111
ZT		Sachse et al., "Concomitant food intake does not significantly influence the pharmacokinetics of the novel, bladder-selective antimuscarinic fesoterodine," 2004, Proceedings of the International Continence Society, 34:580
ZT		Sachse et al., "Safety, tolerability and pharmacokinetics of fesoterodine in patients with hepatic impairment," 2004, Proceedings of the International Continence Society, 34:585
ZT		Sachse et al., "Safety, tolerability and pharmacokinetics of fesoterodine after co-treatment with the potent cytochrome P450 3A4 inhibitor ketoconazole," 2004, Proceedings of the International Continence Society, 34:586
ZT		Sachse et al., "Clinical pharmacological aspects of the novel bladder-selective antimuscarinic fesoterodine, " 2004, Progrès en Urologie, 14 (Suppl. 3):58
ZT		Stahl et al., "Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity," 1995, Neurourol. Urodyn. 14:647-55

EXAMINER ZT Page 5 DATE 14 APRIL 2007

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

ISSUE CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)							
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
514	551	560	140						
INTERNATIONAL CLASSIFICATION									
A01N 37/12									
A01N 37/44									
A61K 31/22									
C07D 69/00									
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(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

2 NOVEMBER 2007

Zachary C Tucker

(Primary Examiner) (Date)

Total Claims Allowed: 7

O.G. Print Claim(s)	O.G. Print Fig.
1 and 4	1

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
11/201,756	MEESE ET AL.
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
11/201,756	MEESE ET AL.	
Examiner	**Art Unit**	
Zachary C. Tucker	1624	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
EAST	**USPG-PUB**	**11/2/2007**	**ZT**
514/551 and 560/140, AS SHOWN ON THE SEARCH HISTORY PRINTOUT			

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
PALM - INVENTORS' NAMES SEARCH UPDATED	11/2/2007	ZT
EAST - USPAT, USPG-PUB, EPO, JPO, DERWENT, FPRS CLASS/SUBCLASSES 514/551 and 560/140, CROSS-REFERENCED WITH TEXT TERMS:	11/2/07	ZT
["DIPHENYLPROPYLAMINE" or "TOLTERODINE"] SEARCH HISTORY PRINTOUT IS IN THE APPLICATION FILE WRAPPER		

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

REQUEST FOR CONTINUED EXAMINATION (RCE)

TRANSMITTAL FORM (37 C.F.R. § 1.114)

DOCKET NO.	APPLICATION SERIAL NO.	EXAMINER	ART UNIT
12961/46103	11/201,756	Tucker, Zachary C.	1624

INVENTOR(S): Meese et al.

Mail Stop: RCE
Commissioner for Patents
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I hereby certify that this correspondence is being deposited with the United States Postal Service via electronic filing addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Date: January 18, 2008
Signature: Theresa A.E. Doonan

This is a **request for continued examination** under 37 C.F.R. § 1.114 (RCE) of pending application Serial No. **11/201,756** filed on **August 10, 2005** entitled ***Novel Derivatives of 3,3-Diphenylpropylamines***

The following constitute the submission **required** by 37 C.F.R. § 1.114(a):

_____ Amendment previously submitted on _____;
_____ Supplemental Information Disclosure Statement
_____ Drawing Changes
__X__ Other Submission: Amendment dated January 18, 2008; Exhibits A-H; Declaration under 37 CFR 1.132 of Dr. Peter J.M. Ney.

Please charge the required RCE and submission filing fee of **$810.00 (large entity)** to the deposit account of **Kenyon & Kenyon LLP**, deposit account number **11–0600**.

The Commissioner is authorized to charge payment of any additional fees required, associated with this communication or arising during the pendency of this application, or to credit any overpayment, to the deposit account of **Kenyon & Kenyon LLP**, deposit account number **11–0600**. A duplicate copy of this transmittal form is enclosed.

Dated: January 18, 2008

Respectfully submitted,

Joseph A. Coppola
Reg. No. 38,413

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Docket No.: 12961/46103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Meese et al.
SERIAL NO.	:	11/201,756
FILED	:	August 10, 2005
FOR	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
EXAMINER:		Tucker
GROUP ART UNIT	:	1624

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COMMISSIONER FOR PATENTS
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AMENDMENT

SIR:

Please consider the following amendments and remarks. Enclosed herewith are:

(1) a Request for Continued Examination,

(2) Exhibits A-H; and

(3) a Declaration under 37 C.F.R. §1.132 of Dr. Peter J.M. Ney.

CLAIM AMENDMENTS

This listing of claims will replace all prior versions and listings of claims in the application:

1-27. (canceled)

28. (previously presented) R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

29. (currently amended) A salt of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ~~and~~ with a physiologically acceptable acid.

30. (currently amended) A pharmaceutical composition comprising an effective amount of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester~~, its~~ or a salt thereof with a physiologically acceptable acid~~, or its free base~~ and a pharmaceutically acceptable carrier.

31. (currently amended) A method of antagonizing a muscarinic receptor in a patient in need thereof, the method comprising ~~contacting the receptor with~~ administering to the patient R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester~~, its~~ or a salt thereof with a physiologically acceptable acid~~, or its free base~~ so as to result in contact of the muscarinic receptor with an effective amount of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol.

32. (currently amended) A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering ~~the~~ to the mammal a pharmaceutical composition ~~of claim 30~~ comprising an effective amount of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a salt thereof with a physiologically acceptable acid.

33. (previously presented) The method according to claim 32 wherein the disease is urinary incontinence.

34. (currently amended) The method according to claim ~~32~~ 33 wherein the mammal is a human.

35. (new) A compound selected from the group consisting of:

acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

36. (new) The compound of claim 35 where the compound is selected from the group consisting of:

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

37. (new) A pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of:

acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl

ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid,

and a pharmaceutically acceptable carrier.

38. (new) The pharmaceutical composition of claim 37 where the compound is selected from the group consisting of:

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

39. (new) A method of treating a disease or condition in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering to the mammal a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of:

acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

40. (new) The method of claim 39 where the compound is selected from the group consisting of:

n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

41. (new) The method of claim 39 or 40 where the disease or condition is a spasmogenic condition that is caused by a muscarinic mechanism.

42. (new) The method of claim 39 or 40 where the disease or condition is urinary incontinence.

43. (new) The method of claim 42 where the mammal is a human.

Remarks

Prior to this Amendment, claims 28-34 were pending. By this Amendment, new claims 35-43 have been added. Accordingly, claims 28-43 are now pending.

Claim 30 has been amended to delete recitation of "free base" since this term was merely a harmless duplication of the subject matter expressed by the recited chemical name. Claim 31 has been similarly amended. Claim 30 has also been amended to recite "pharmaceutically acceptable carrier." Support for this recitation is found in the specification, at page 35, 3rd paragraph, lines 8-9.

Claim 31 has been amended to recite administering R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a salt thereof with a physiologically acceptable acid so as to result in contact of the muscarinic receptor with the active metabolite R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol. Support for this amendment can be found in the specification at page 91, line 24, to page 92, line 30.

Claim 32 has been amended to independent form.

New claims 35-43 have been added and are directed to compounds, compositions, and methods relating to the group of compounds disclosed in Figure 1.

Support for new claims 35, 37, and 39 is found in Figure 1 (recitation of individual compounds) and in the specification at page 6, 4th paragraph from bottom (racemic mixtures, individual enantiomers, and salts). The compounds in these claims may be in the form of a racemic mixture or as an individual enantiomer, and the

compounds (whether individual enantiomers or mixtures of enantiomers) may be in the form of salts.

New claims 36, 38, and 40 depend from new claims 35, 37, and 39, respectively, and recite the compounds of new claims 35, 37, and 39 that are phenolic monoesters. Support for new claims 36, 38, and 40 is found in Figure 1 and in the specification at pages 10-12, which teaches preferred compounds of the invention that are phenolic monoesters.

Support for new claims 41 and 42 is found in the specification at page 36, 3rd paragraph, 1st sentence.

Terminal Disclaimers

With the Amendment filed October 22, 2007, the Applicants filed four Terminal Disclaimers. The Terminal Disclaimers were all signed by Dr. F. Dressen,[1] Senior Patent Counsel of the assignee, Schwarz Pharma AG.

The Applicants refer to reel 011443, frame 0478, of the assignment records of the U.S. Patent and Trademark Office, where an assignment of the entire right, title, and interests of the parent application, U.S. Patent Application Serial No. 09/700,094, as well as all its continuation and divisional applications, from the inventors to Schwarz Pharma AG is recorded. The present application is a continuation of a continuation of U.S. Patent Application Serial No. 09/700,094.

[1] Dr. Dressen, who is German, spelled his last name using the German symbol for double s, i.e., "ß."

Dr. F. Dressen is empowered to sign terminal disclaimers on behalf of the assignee, Schwarz Pharma AG.

New claims

New claims 35-43 have been added and are directed to compounds, compositions, and methods relating to the group of compounds disclosed in Figure 1. The Applicants note that the third entry from the left in Table 1 is the compound isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

This group of compounds is patentable because, *inter alia*, it comprises compounds that are especially well cleaved by human liver S9 fraction to give good levels of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, while certain related compounds are not well cleaved. Exhibit A, to the attached Declaration of Dr. Peter Ney, shows a table of results for S9 cleavage for the compounds of new claims 35-43 as well as for other, related compounds. Exhibit A shows unexpectedly superior cleavage results for the claimed compounds.

Figure 1 of the present application was based on Exhibit A and thus Exhibit A was available as of the filing date of EP 98108608, filed on May 12, 1998.

Further evidence of the superior properties of the compounds of new claims 35-43 is provided by Ney Exhibit B. Exhibit B contains additional data with respect to the ability of certain compounds to be cleaved by the human S9 liver fraction. Exhibit B was available as of the filing dates of U.S. Patent Application Serial No. 10/766,263 (now U.S. Patent No. 7,230,030); U.S. Patent Application Serial No. 09/700,094 (now U.S. Patent No. 6,713,464); and International Patent Application PCT/EP99/03212.

The Applicants would like to point out a small inconsistency between the table at page 93 of the present application and data that were in the possession of the Applicants at the time of the May 11, 1999 filing date of International Patent Application PCT/EP99/03212 and that were used to prepare the table on page 93.

Ney Exhibit C shows the data that were used to prepare the table on page 93. Comparison of Exhibit C with the table shows that one entry in Exhibit C (SPM 6725, (+)-AcO/OBz x HCl) was omitted from the table on page 93. Also, the IC_{50} value for the entry for (+)AcO-/-OiBut was mistakenly reported in the table on page 93 as 240 nM rather than the correct entry shown in Exhibit C, 35 nM. 240 nM is the correct entry for the omitted compound, (+)-AcO/OBz x HCl.

While the Applicants continue to believe that the skin permeation properties of isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester are excellent and that the table at page 94 of the present application is accurate, in the interests of complete disclosure, the Applicants submit Ney Exhibit D. Exhibit D shows data similar to the data of the table on page 94, but also shows data for the pivalate diester (fourth entry from top) indicating that the pivalate diester does not permeate through human skin. Exhibit D was available as of the May 11, 1999 filing date of International Patent Application PCT/EP99/03212.

Exhibit E is also being submitted in the interests of complete disclosure. Exhibit E is an internal report generated by Schwarz Pharma AG, the assignee of the present application, that was prepared about April of 2002 that discusses various aspects of the permeation properties through mouse and human skin for certain compounds. Exhibit E became available during the pendency of International Patent

Application PCT/EP99/03212, U.S. Patent Application Serial No. 10/766,263, and U.S. Patent Application Serial No. 09/700,094.

The enclosed Declaration under 37 C.F.R. §1.132 of Dr. Ney explains certain aspects of the enclosed Exhibits A-D.

The Applicants attach to this Amendment copies of U.S. Patents Nos. 6,713,464, 6,858,650 and 7,230,030 (mentioned in the Terminal Disclaimers discussed above) as Exhibits F, G and H, respectively, in order to enable the Examiner to easily assess the Terminal Disclaimers and the claims in said patents compared with the claims presented herein as well as the data in Exhibits A-E.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

The Examiner is invited to contact the undersigned should any question arise concerning this Amendment or the accompanying Ney Declaration.

Respectfully submitted,

Date: JANUARY 18, 2008 BY: 

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Attorney Docket No. 12961/46103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Meese et al.
SERIAL NO.	:	11/201,756
FILING DATE	:	August 10, 2005
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EXAMINER	:	Tucker
GROUP ART UNIT:		1624

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. PETER J.M. NEY UNDER 37 C.F.R. § 1.132

I, Dr. Peter J.M. Ney, Ph.D., declare the following:

1. I am a German citizen residing at Kirchstrasse 71, 41517 Grevenbroich, Germany.

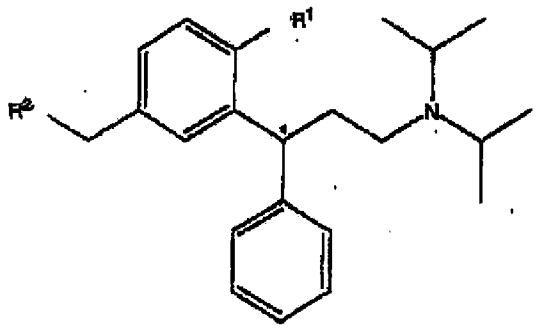
2. I am currently working as Associate Director Pharmacology at Schwarz BioSciences GmbH. Schwarz BioSciences GmbH is a wholly-owned subsidiary of Schwarz Pharma AG, the assignee of U.S. Patent Application Serial No. 11/201,756. I was employed by Schwarz Pharma AG and was the project team leader during the initial synthesis and investigation phase of the compounds claimed in U.S. Patent Application Serial No. 11/201,756.

3. I have been provided with copies of documents that I am informed are to be filed in connection with the prosecution of U.S. Patent Application Serial No. 11/201,756. These documents are attached hereto as Exhibits A-D.

4. I have first hand knowledge of the information contained in Exhibits A-D through my work at Schwarz Pharma.

5. Exhibit A shows the amount of the racemic form of the active metabolite (R,S-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, referred to as "SPM 7500") produced in human liver S9 incubated with the compounds (referred to as "prodrugs") listed along the bottom of Exhibit A.

6. The compounds listed along the bottom of Exhibit A can be represented as derivatives of the following general structure:



7. For the compounds listed at the bottom of Exhibit A,
AcO-/-OAc is the acetyl diester (i.e., both R^1 and R^2 are AcO);
HO-/-OBut is the phenolic butyryl ester (i.e., R^1 is OBut and R^2 is OH);

HO-/OiBut is the phenolic isobutyryl ester (i.e. R^1 is OiBut and R^2 is OH) [R,S- isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester];

iButO-/-OiBut is the isobutyryl diester (i.e., both R^1 and R^2 are iButO);

ButO-/-OBut is the butyryl diester (i.e., both R^1 and R^2 are ButO);

PropO-/-OProp is the propionyl diester (i.e., both R^1 and R^2 are PropO);

HO-/-OProp is the phenolic propionyl ester (i.e., R^1 is OProp and R^2 is OH);

HO-/-OAc is the phenolic acetyl ester (i.e., R^1 is OAc and R^2 is OH);

HO-/-OPiv is the phenolic pivaloyl ester (i.e., R^1 is OPiv and R^2 is OH);

EtO-/-OHxMesylat is the mesylate salt of the benzylic ethyl ether (i.e., R^1 is OH and R^2 is EtO);

MeO-/-OH is the benzylic methyl ether (i.e., R^1 is OH and R^2 is MeO);

iButO-/-OBn is the benzylic isobutyryl ester/phenolic benzyl ether (i.e., R^1 is BnO and R^2 is iButO);

OH-/-OBn is the phenolic benzyl ether (i.e., R^1 is BnO and R^2 is OH);

AcO-/-OBn is the benzylic acetyl ester/phenolic benzyl ether (i.e., R^1 is BnO and R^2 is AcO);

EtO-CO-O-/-O-CO-OEt is the ethyl dicarbonate (i.e., both R^1 and R^2 are EtO-CO-O);

TBDMSiO-/-OH is the benzylic t-butyl dimethyl silyl ether (i.e., R^1 is OH and R^2 is TBDMSiO);

PivO-/-OPiv is the pivaloyl diester (i.e., both R^1 and R^2 are PivO);

BzO-/-OBn is the benzylic benzoyl ester/phenolic benzyl ether (i.e., R^1 is BnO and R^2 is BzO);

HO-/-OCONHEt is the phenolic ethyl carbamate (i.e., R^1 is OCONHEt and R^2 is OH); and

EtNHCO-O-/-O-CONHEt is the ethyl dicarbamate (i.e., both R^1 and R^2 are EtNHCO-O);

8. Exhibit B shows additional data pertaining to the amount of the racemic form of the active metabolite produced in human liver S9 incubated with certain compounds. The second column from the right indicates the amount of the racemic form or of the respective enantiomer of the active metabolite produced by the various compounds. One asterisk

indicates little amount of the racemic form of the active metabolite produced; three asterisks indicate a large amount of the racemic form of the active metabolite produced.

9. The English translations of the German phrases appearing in the rightmost column of Exhibit B are as follows:

"Nebenprodukte" = by-products

"fraglich, kein OH/OH" = questionable, no active metabolite

"wenig Umsatz" = little conversion, i.e., not much active metabolite produced

"enth. PhCOOH" = contains benzoic acid

"sehr instabil" = very unstable

"fragl., vermutl. instabil" = questionable, presumably unstable

Struktur fraglich = structure questionable

10. Exhibit C describes the results of studies to determine the binding of the indicated compounds to human M_2 and M_3 muscarinic receptors as well as the ability of those compounds to reduce / antagonize methacholine-induced contraction of the guinea pig ileum.

11. The compounds tested in Exhibit C were derivatives of the general structure shown in paragraph 6 above where:

(+)-HO/OH x HCl is the hydrochloride salt of the active R-isomer of the metabolite (i.e., both R^1 and R^2 are OH);

(-)-HO/OH x HCl is the hydrochloride salt of the less active S-isomer of the metabolite (i.e., both R^1 and R^2 are OH);

(+)-BzO/OBz x HCl is the hydrochloride salt of the R-isomer of the benzoyl diester (i.e., both R^1 and R^2 are BzO);

(+)-AcO/OBz x HCl is the hydrochloride salt of the R-isomer of the benzylic acetyl ester/phenolic benzoyl ester (i.e., R^1 is BzO and R^2 is AcO);

(+)-OH/OiBut x HCl is the hydrochloride salt of the R-isomer of the phenolic isobutyryl ester (i.e. R^1 is OiBut and R^2 is OH); [R-(+)- isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester];

(+)-AcO/OiBut x HCl is the hydrochloride salt of the R-isomer of the benzylic acetyl ester/phenolic isobutyryl ester (i.e., R^1 is iButO and R^2 is AcO);

(+)-OH/OBz x HCl is the hydrochloride salt of the R-isomer of the phenolic benzoyl ester (i.e., R^1 is BzO and R^2 is OH);

(+)-(R)-H/OH x (L)-(+)-Tartrate is the L-tartrate salt of the R-isomer of tolterodine (INN).

12. In Exhibit D, the references to "Tolt." in the third column refer to tolterodine.

Statements herein based on my own knowledge are true. I acknowledge that willful false statements are punishable by fine or imprisonment as provided for by 18 U.S.C. § 1001 and may jeopardize the validity or enforceability of any patent that may mature from the present Application.

Signed January 18, 2008

P. Ney

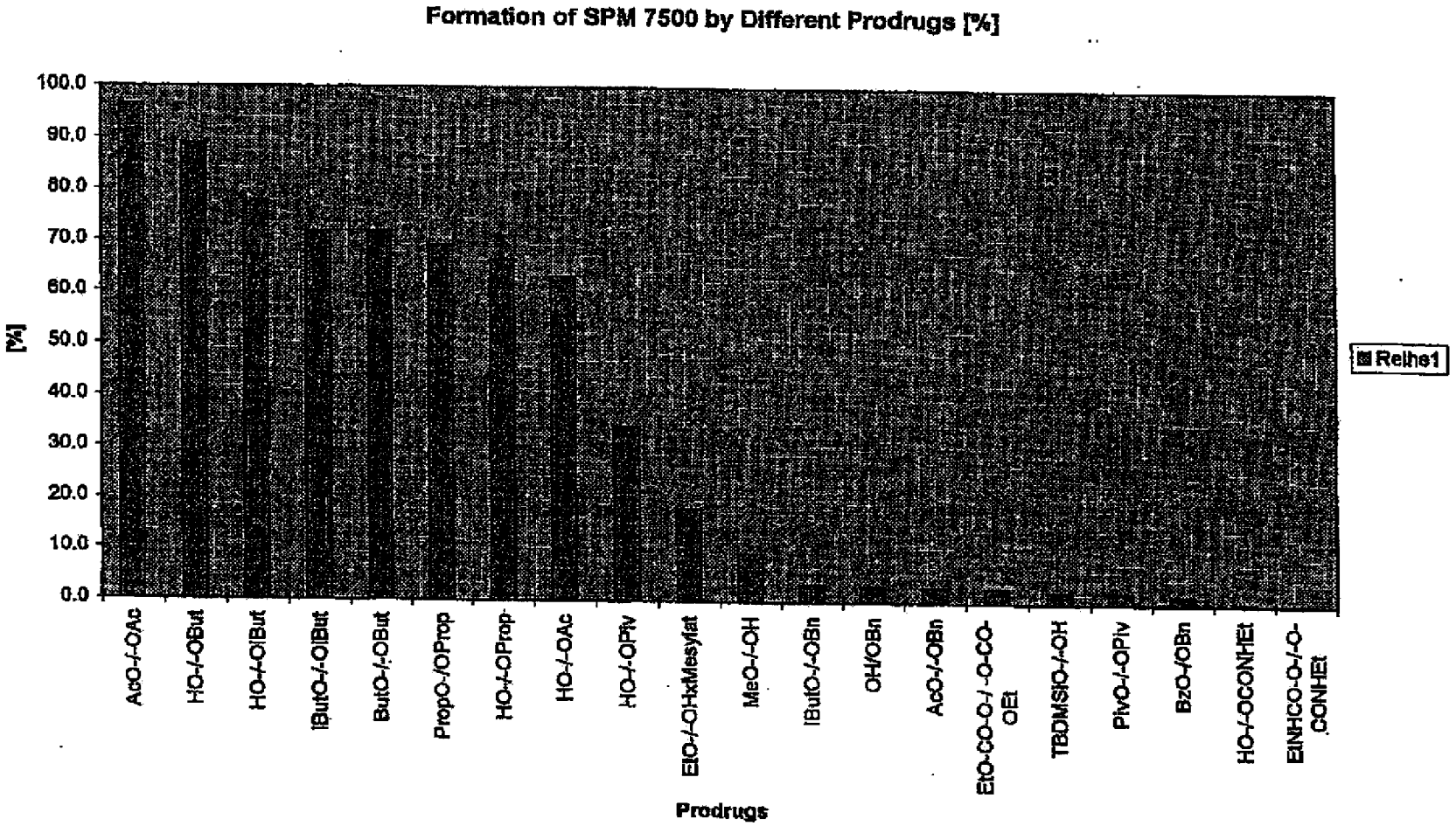
Dr. Peter J.M. Ney

ATTORNEY DOCKET NO. 12961/46103

US PATENT APPLICATION NO. 11/201,756
Novel Derivatives of 3,3-Diphenylpropylamines

EXHIBIT A

S9 Diagr.



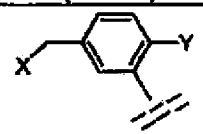
ATTORNEY DOCKET NO. 12961/46103

US PATENT APPLICATION NO. 11/201,756
Novel Derivatives of 3,3-Diphenylpropylamines

EXHIBIT B

SPM- / Substanz-Liste nur S9

Nomenklatur: (X- / -Y)



SPM	Charge	Struktur	MW [g/mol]	MS-Spektr.	HPLC-Geh. [%]	Stabilität pH 7,4 über 24h/RT	Stabilität pH 3,0 über 24h/RT	Stabilität Plasma	S9-Inkub. 1 h	Bem. zu S9
6645	RK-6645	MeO-/-OH	355.53						**	Nebenprodukte !
6647	RK-6647	HO-/-OCONHEt	412.58			stabil	stabil		?-	fraglich, kein OH/OH
6648	RK-6648	EtO-/-OH	369.55						*	Nebenprodukte !
6650	RK-6650/1	AcO-/-OAcxHCl	462.03	vorh.					***	
6651	RK-6651/1	EtO-/-OEtMesylat	465.66			stabil	stabil		*	Nebenprodukte
6652	RK-6652/2	HO-/-OCONHEtxHCl	450.05		93,342				?-	fragl. kein OH/OH
6653	RK-6653/1	MeO-/-OHxHCl	391.99							
6656	RK-6656/2	EtO-/-OHxHCl	406.01							
6661	RK-6661	HO-/-OCONHButHNOCO-/-OHx2HCl	696.06		84,98				?-	fragl. kein OH/OH
6681	RK-6681	HO-/-OEt	369.55							
6690	RK-6690	EtO-/-OBzxHCl	510.12			t 1/2 = 29.6 h	stabil		*	Nebenprodukte
7461	RD-7461	H-/-OH	339.53	vorh.						
7468	RD-7468	HO-/-OBn	431.62						*	
7468	AC-8124									
7468	AC-8125									
7468	AC-8129									
7471	RD-7471	BzO-/-OBn	535.73			t 1/2 = 0.9 h	stabil		*	wenig Umsatz
7472	RD-7472	tButO-/-OBn	501.71			t 1/2 = 6.5 h	stabil		*	wenig Umsatz
7477	RD-7477	AcO-/-OtBut	453.63			stabil	stabil		***	
7496	RD-7496	HO-/-OPiv	425.62			stabil	stabil		*	wenig Umsatz
7497	RD-7497	HO-/-OPivxHCl	462.08						*	wenig Umsatz
7500	AC-8127	HO-/-OH	341.5							
7500	AC-8137			vorh.						
7500	AC-8140									
7500	AC-8160					stabil	stabil			

7500	AC-8190									
7500	AC-8191									
7500	RD-7483								-	wenig Umsatz
7500	RD-7488									
7501	RK-6638/a	AcO-/-OAc	425.57	vorh.					***	
7501	RK-6650			vorh.		stabil	stabil			
7502	FP-9061	tButO-/-OtBut	481.68	vorh.		t 1/2 = 41.3 h	stabil		***	
7502	FP-9064	tButO-/-OtBut	481.68							
7503	AC-8158	PivO-/-OPiv	509.74	vorh.		t 1/2 = 9.3 h	stabil		*	Wenig Umsatz
7503	AC-8161									
7504	RD-7475	HO-/-OtBut							***	
7504	FP-9060	HO-/-OtBut	411.59	vorh.		stabil	stabil		***	
7504	FP-9066	HO-/-OtBut	411.59							
7511	RD-7511	HO-/-OProp	397.56			stabil	stabil		***	
7512	RD-7512	HO-/-OBut	411.59			stabil	stabil		***	
7513	RD-7513	HO-/-OAc	383.54			stabil	stabil			
7513	FP-9063	HO-/-OAc	383.54						***	
7514	RD-7514	PropO-/-OProp	453.63			stabil	stabil		***	
7515	RD-7515	ButO-/-OBut	481.68			t 1/2 = 28.0 h	stabil		***	
7519	RD-7519	HO-/-OAcxHCl	420.00						***	
7520	RD-7520	HO-/-OPropxHCl	434.02						***	
7521	RD-7521	HO-/-OButxHCl	448.05						***	
7522	RD-7522	ButO-/-OButxHCl	518.14						***	
7523	RD-7523	PropO-/-OPropxHCl	490.09						***	
7527	RD-7527	HO-/-OtButxHCl	448.05						***	
7528	RD-7528	tButO-/-OtButxHCl	518.14						***	
7569	RD-7569	BzO-/-OBz	549.72			t 1/2= 1.5 h	stabil		***	enth. PhCOOH
7569	AC-8195									
7570	RD-7570	HO-/-OBz	445.61			stabil	stabil		***	
7570	AC-8196									
8132	AC-8132	AcO-/-OBn	473.66			t1/2= 11.8 h	stabil		*	wenig Umsatz
8132	AC-8135								*	
8143	AC-8142	AcO-/-OH	383.54							sehr instabil
8143	AC-8143			vorh.						
8143	AC-8144									
8143	AC-8145			vorh.						
8146	AC-8146	ButO-/-OH	411.59	vorh.					-	sehr instabil

8148	AC-8148	BzO-/-OH	445.61			$H_2$0,5%,DI-OH,8h	stabil		-	fragl., vermutl. instabil
8150	AC-8152	iButO-/-OH	411.59							sehr instabil
8150	AC-8150			vorh.			stabil			
8151	AC-8151	PivO-/-OH	425.62			t 1/2 < 10 min	stabil		-	sehr instabil
8163	AC-8163	HO-/-OHxHCl	377.86			stabil	stabil			
8163	RD-7517									
8163	AC-8165									
8168	AC-8166	PivO-/-OPivxHCl	546.19						*	wenig Umsatz
8193	AC-8192	d2-HO-/-OH	343.51	vorh.						
8193	AC-8193			vorh.						
8193	AC-8194									
-	AC-8202	HO2C-/-OH	355.48							
9052	FP-9052/1	TBDMSIO-/-OTBDMSI	570.03	vorh.					-	
9053	FP-9053	TBDMSIO-/-OH	455.76	vorh.					*	wenig Umsatz
9055	FP-9055/1	HO-/-OTBDMSI	455.76						*	wenig Umsatz
9056	FP-9056/1	EtNHCO-O-/-OTBDMSi	526.84	vorh.					-	
9057	FP-9057	EtNHCO-O-/-OH	412.56						-	
9058	FP-9058	EtNHCO-O-/-O-CONHEt	483.66	vorh.		stabil	stabil		+	wenig Umsatz
9059	FP-9059	EtO-CO-O-/-O-CO-OEt	483.63	vorh.					?-	Struktur fraglich ?
9062	FP-9062	HO-/-OHxMandelat-D,L	493.65							
9069	FP-9069	HO-/-OHxTartrat-D,L	491.59							
9070	FP-9070	HO-/-OHxMalat-D,L	475.59							
9075	FP-9075	rac H-/-OH x HCl	361.96							
9078	FP-9078	(R) H-/-OH L-Tartrat	475.59							
9080	FP-9080	(R) H-/-OH	325.5							
9081	FP-9081	(R) H-/-OAc	367.54			stabil	stabil		***	
9082	FP-9082	(R)H-/-OBz	429.61			t 1/2 = 14.4 h	stabil		***	enth. PhCOOH
9084	FP-9084	rac d5- H-/-OH x HCl	366.99							
9085	FP-9085	(R)-d4(?)-H-/OH-L-Tartrat	479.61							
9086	FP-9086	(S) H-/-OH-D-Tartrat	475.59							
9087	FP-9087	rac-H-/-OH	325.5							
9088	FP-9088	(S) H-/-OH	325.5							
9089	FP-9089	(R) H-/OH d4(?)	329.5	vorh.						
9090	FP-9090	(S)-d4(?)-H-/-OH D-Tartrat	479.61							
9096	FP-9096	(rac)H-/-OtBut	395.59			t 1/2 = 53.5 h	stabil		***	

Ester										
OAc = Acetat	OiBut = Iso-Butyrat									
OBut = Butyrat	OBz = Benzoesäureester									
OPiv = Pivalat	OProp = Propionat									
Ether										
OBn = Benzyl-ether	OEt = Ethoxy	OMe = Methoxy								
Sonstige funktionelle Gruppen										
HO = Hydroxy	CH3 = Methyl									
Bz = Benzoyl										
TBDMSiO oder OTBDMSi = tert-Butyldimethylsilylether										
EtNHCO-O oder O-CONHEt = Carbamat										
EtO-CO-O oder O-CO-OEt= Carbonat										
Salze										
HCl = Hydrochlorid										
Mesylat = Methansulfonsäuresalz										
Mandelat = Mandelsäuresalz										
Tartrat = Weinsäuresalz										
Malat = Äpfelsäuresalz										
Legende zu S9-Inkubationen: *, **, *** wenig bis vollständige Bldg. von -OH/-OH										
- keine Spur (siehe auch Bemerkungen)										

EXHIBIT C

Peter Ney, NPTA

04.06.1999

Data on NCE- Incontinence Substances (SPM007)

Substance	abbrev. name	M_2 receptor binding		M_3 receptor binding		guinea pig ileum antagonism	
		IC_{50} [nM]	K_i [nM]	IC_{50} [nM]	K_i [nM]	% at 30 µM	IC_{50} [µM]
SPM 5427	(+)-HO/OH x HCl	6.7	2.4	8.7	1.2	100	0.02
SPM 5428	(-)-HO/OH x HCl	66.7	23.7	1300	181.3	97	0.68
SPM 6723	(+)-BzO/OBz x HCl	594	211.4	2400	334.7	100	0.22
SPM 6725	(+)-AcO/OBz x HCl	1500	533.8	5400	753.1	100	0.24
SPM 8228	(+)-HO/OiBut x HCl	6.2	2.2	159.3	22.2	100	0.057
SPM 8229	(+)-AcO/OiBut x HCl	664.5	236.5	3600	502.1	100	0.035
SPM 8230	(+)-HO/OBz x HCl	32.7	11.6	171.8	24	100	0.18
SPM 9078	(+)-(R)-H/OH x (L)-(+)-Tartrate	45.9	16.3	76.3	10.6	100	0.019

q:\npta\ney\spmdata2.doc

EXHIBIT D

Comparison of permeation through hairless mouse skin and human skin in-vitro with different active drugs of SPM 007

Batch	Drug Code no.	Active Drug	Permeation through hairless mouse skin [µg/cm²/24 h]	Permeation through human skin [µg/cm²/24 h]	Lag-time [h]
INZ 001	SPM 7514 SPM 7511 SPM 7500	DI-Prop Mono-Prop DI-OH	244	70 8 (s.c.)	11,2 9,2
INZ 002	SPM 7500	DI-OH	486	3 2,1 26 (s.c.)	> 36 17,2 17,2
INZ 003	SPM 7502 SPM 7504 SPM 7500	DI-IsoBut Mono-IsoBut DI-OH	201	60 5,8 (s.c.)	9,8 15,1
INZ 004	SPM 7503 SPM 7499 SPM 7500	DI-Piv Mono-Piv DI-OH	39	0	0
INZ 005	SPM 7504 SPM 7500	Mono-IsoBut DI-OH	380	163,8 13 37,4 (s.c.)	36 14,7 5
INZ 006	SPM 9080	R(+) Tolt.	351	303,7	12,9
INZ 007	SPM 9087	R,S Tolt.	429	507,9	14,1
INZ 008	SPM 9094 SPM 9087	R,S Tolt. acetat	418	158,1	9,7
INZ 009	SPM 9095 SPM 9087	R,S Tolt. benz.	205	172,1	9,7
INZ 010	SPM 9096 SPM 9087	R,S Tolt. 2-napr.	418	160,4	11,8
INZ 011	SPM 7501	DI-Acetat	258	58,6	10,2
INZ 012	SPM 6648	Ethylether	438	328,9	29,5
INZ 013	SPM 9089	R(+) Tolt. D_4	572	340,5	10,7
OBU 44 *OBU 55*	*Oxybutynin* *Oxybutynin*		*232* *171*	*122* *150*	*4,7* *11,4*

EXHIBIT E

1. SUMMARY

The report describes in vitro skin permeation characteristics of transdermal delivery systems (TDS) containing Fesoterodine related prodrugs from the SPM907 series. Test samples were prepared by either lab-scale solvent coating or hot-melt processing. Patches were tested by means of flux rates across hairless mouse skin, selected samples were subsequently investigated in the LACDR human skin model.

Initial experiments were performed in 1998/99 with TDS containing racemic mixtures of different produgs. While good drug permeation across mouse skin was found, flux rates across human skin were surprisingly low.

Due to the availability of pure enantiomers some of the prodrugs were reinvestigated in this feasibility study to find out the reason for low human skin permeation. The old flux data across mouse skin could be confirmed and in some cases increased. The low human skin permeations were found to be caused by the LACDR skin model setup. In this model the fresh human skin has to be supported by an additional synthetic membrane. The fresh skin most probably led to partial drug hydrolysis and/or protonation, while the supportive silicone membrane used is known to be impermeable for charged molecules. Replacing this membrane with a dialysis membrane increased the measured flux rates across human skin by a factor of at least 4 to 6. Therefore, the change to the human skin-dialysis membrane composite represents a more realistic estimation of the potential in vivo performance.

Besides the already reported free base of Fesoterodine, the diacetic acid ester prodrug seems to be a suitable transdermal candidate based on these new in vitro flux data.

Distribution: Original PH DOK
F&T, PHA, TS, TT, PH REG, IPM (AS)
Summary only: PCD, PH TOX, BA, MOBI, SIL, ILF

Key words:
Fesoterodine, SPM907 prodrugs, skin permeation in vitro, mouse skin, human skin

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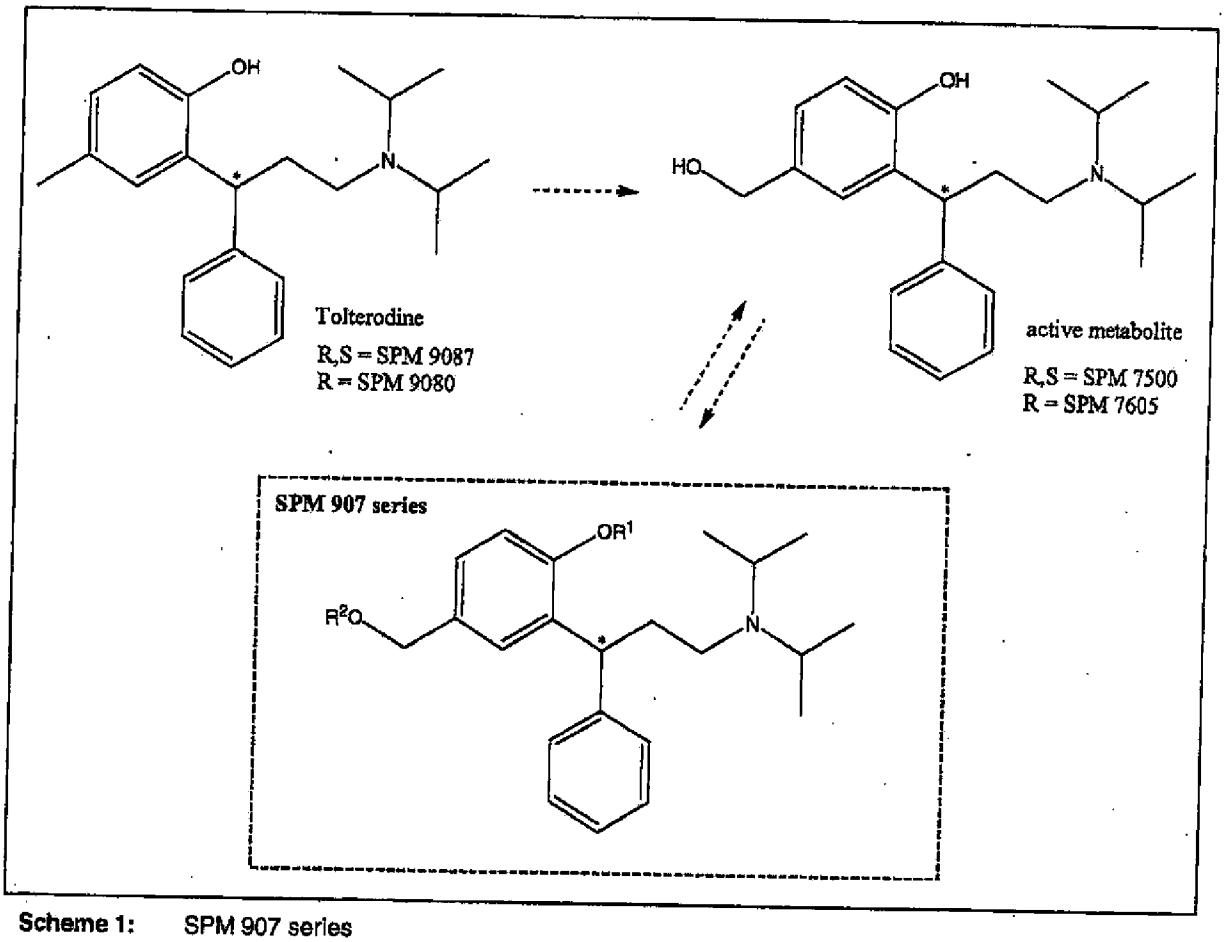
CONTENTS

2. INTRODUCTION AND OBJECTIVES

It is well known, that the hydroxy metabolite of Tolterodine is equipotent to the parent drug [1]. Therefore, several ester prodrugs of this metabolite, the SPM 907 series (scheme 1 and table 1) were synthesized by SIL [2] and subsequently tested for their ability to be delivered transdermally.



Scheme 1: SPM 907 series

Table 1: Assignment of some prodrugs of the SPM 907 series

R^1	R^2	R,S racemic mixture	R enantiomer
H	H	SPM 7500	SPM 7605
H	iBut	SPM 7504	fumarat salt = SPM 8272 = **Fesoterodine** SPM 8224 = **free base of Fesoterodine**
iBut	iBut	SPM 7502	SPM 7675
Ac	Ac	SPM 7501	SPM 8302

iBut → iso-butyric acid ester, Ac → acetic acid ester

Initial experiments performed in 1998/99 with racemic mixtures of the prodrugs revealed that they can be embedded into a solvent coated acrylic based TDS and that most of them possess the ability to permeate across hairless mouse skin with suitable flux rates. But, surprisingly, in many cases only low flux rates across human skin in the LACDR skin model [3] were found.

Due to the availability of pure enantiomers and a broader variety of patch compositions some of the prodrugs were re-investigated to find out the reason for low human skin permeation. Therefore, lab-scale batches of hot-melt and solvent coated patches were prepared and initially tested in a mouse skin model. Subsequently, some of the patches were investigated in the LACDR human skin model.

3. MATERIALS AND METHODS

For a detailed description of the experiments refer to the batch documentation.

Hot-melt patches (exemplary): 8 g of a preformed silicone adhesive were weighed into a beaker and tempered at 160°C for ca. 20 min to achieve a homogenous melt. 0.5 g of inner phase polymer (e.g. poly(ethylene oxide) and 1.5 g of drug were added. After tempering at 160°C for additional 5 min the mixture was homogenized manually and further processed on the pre-tempered Chill-Roll (120°C, 250 µm) for lamination.

5 cm^2 patches were isolated by manual punching followed by determination of the average patch weight (n=10). Finally, patches were sealed individually in pouches.

Mouse Skin Model (PHA): according to OBU0469.ABV100, rev. 00 (1998) with an active diffusion area of 2.55 cm^2, a phospate buffer acceptor phase at pH 6.2 and a temperature of 32°C, n=3

Human Skin Model (LACDR):

according to H. Tanojo et al. , J. Control Rel. 45 (1997) 41-47.

skin from abdomen with a thickness of approx. 250 µm, flux experiment: acceptor phase: PBS, pH= 6.2, temperature: 32ºC, diffusion cells with spiral groove (8 cells), groove area: 0.552 cm^2, dialysis membrane used as separator between skin and acceptor phase

flux: 5 ml/hour PBS, experiment runs for 72 hours, sampling cycle: 3 hours

Analytical Methods (PHA): refer to certificates of analysis

Data Analysis: sigmoidal Bolzmann and linear fit: Microcal Origin 6.0

4. RESULTS AND DISCUSSION

Racemic mixtures of the prodrugs (review of historic data)

Thirteen patch batches containing different racemic prodrugs of the SPM907 series as well as Tolterodine and Tolterodine prodrugs were initially embedded into acrylic-type polymers by a lab-scale solvent coating procedure. Tributyl citrate was added as plasticizer. All patches were investigated in both, the internal hairless mouse skin model and the LACDR human skin model. Table 2 summarizes some of the re-calculated former data.

Table 2: Solvent coated patches (with a theoretical drug content of 15% (w/w))

No	Lot No (Ch.B.)	Lot No (old)	Drug (SPM Code)	Permeation [1] Mouse Skin (n=4) [µg/(cm² 24h)]	Permeation [1,2] Human Skin [µg/(cm² 24h)]	Mouse : Human Skin Perm. Ratio
1	20002006	INZ 003	Di-iBut (7502)	155.54	43.64 / lag time ~14 h	3.56
2	20002008	INZ 005	iBut (7504)	496.87 [3]	193.31 / lag time ~34 h	2.57
3	20002005	INZ 002	Di-OH (7500)	689.21 [3]	5.96 / lag time ~38 h	115.64
4	20002014	INZ 011	Di-Ac (7501)	363.26 [3]	45.10 / lag time ~11 h	8.05

1) In case of SPM907 prodrugs re-calculated as permeation of active metabolite Di-OH (SPM 7500)

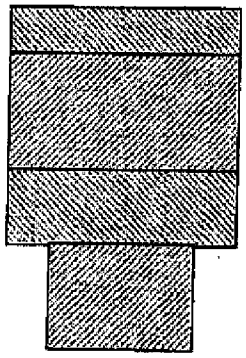
2) In case of SPM907 prodrugs calculated without consideration of the (low) amounts of hydrolysis products

3) non-linear release kinetics, calculated from the linear part in the period of 0-30 h

The observed permeation rates for most of the SPM907 prodrugs across mouse skin were suitably high. In case of the di-iso-butyric acid ester (No 1, table 2) steric hindrance most probably caused a lower value.

The flux rates across human skin decreased in the following order: iBut >> DiAc, DiBut >> DiOH. While the very low flux rate of SPM7500 (DiOH) could be caused by the hydrophilicity of this molecule, the low flux rates of SPM7501/2 (DiAc/DiBut) were surprising. To get a better understanding of these human skin permeation results a more detailed knowledge of the LACDR human skin model is necessary. In this model the skin is not in direct contact with the acceptor medium, since it has to be stabilized with an additional membran. A silastic sheeting (silicone membrane) was used in the oder experiments described above to support the skin (compare scheme 2).

Scheme 2: LACDR experimental setup



patch, area = 2.545 cm²

human skin, area = 2.545 cm², ~ 250 µm

silicone membrane, area = 2.545 cm², 150 µm

diffusion cell, area = 1.131 cm²
with spiral grooves, area = 0.552 cm²

Due to this setup always two experiments have to be performed: one to determine the flux of the active across the supportive membrane and a second one to determine the flux across the 'composite' of human skin and supportive membrane. The obtained values of the barrier properties of the supportive membrane are used to correct the values of the second experiment.

In all experiments acceptable high flux rates for the SPM907 prodrugs across the supportive membrane were found (comp. Annex), although the permeability of the silicone membrane decreased in the following ranking order: Di-But > iBut > DiAc > Di-OH, possibly due to increasing hydrophilicity. Nevertheless, all values were high enough and therefore, acceptable for the determination of the barrier properties of the silastic sheeting.

From the data obtained in the experiments with the human skin - supportive membrane composite it can be stated, that a) the flux of the active metabolite (DiOH, No 3 table 2) was generally quite low and b) the flux of the racemic free base of Fesoterodine (iBut, No 2 table 2) would theoretically enable the delivery of nearly 4 mg/24 h from a 20 cm^2 patch across human skin.

Nevertheless, the partially extremely low flux rates found for the ester prodrugs indicate secondary processes taking place. Since in the LACDR model fresh human skin is used, it is likely that metabolic/enzymatic activity is still present. Thereby induced ester hydrolysis will immediately generate charged molecules, which are no longer able to permeate across the supportive membrane (compare next paragraph). In conclusion, these older data do not assess the human skin permeation of all SPM907 (pro)drugs accurately.

R-enantiomers

As already reported [4] Fesoterodine and some of the prodrug enantiomers were investigated by controlled melt embedding (temperature range of 25-150°C) to assess the drug excipient compatibility under hot-melt conditions. 1:1 mixtures of drug and excipient showed no signs of degradation under the test conditions enabling patch preparation by hot melt techniques.

SPM7605 (DiOH)

SPM7605 is the main hydrolysis product and active metabolite of Fesoterodine and related prodrugs from the SPM907 series. The colorless powder is characterized by a melting point in the range of ~101-102°C and a purity or more than 99%. More than 10 lab-scale batches of hot-melt patches were prepared without encountering any difficulties. Table 3 summarizes some of the results obtained in the mouse skin model.

Table 3: SPM7605 hot melt patches

No	Lot No. (Ch.B.)	PSA	Theo. Drug Loading [% w/w]	Mouse Skin Perm. [µg/(cm² 24 h)]
1	20008029	SxS	10	261.55 [1)]
2	20008030	SxS	10	274.32 [1)]
3	20106045	EVA	15	220.87 [1)]
4	20106043	BioPSA/PEO	15	384.04 [1)]

1) non-linear release linetics, calculated from the linear part in the period of 0-30 h

SxS: styrene-block-copolymer, EVA = ethylene vinyl acetate copolymer,

BioPSA/PEO = silicone pressure sensitive adhesive containing additional 5% poly(ethylene oxide)

From these data it can be concluded that the flux rates of the pure enantiomer SPM7605 across mouse skin were still in a suitable range, although the observed values were generally lower than those obtained with the racemic mixture, SPM7500 (No 3 table 2). The most likely explanation is the difference of the patch compositions used.

No 4 (table 3) was investigated in the LACDR human skin model (for flux data comp. Annex). Already the flux across the supportive silastic sheeting was lower than across mouse skin, therefore, the flux across the composite of human skin plus membrane was negligible. The corrected value for human skin was found to be 2.3 µg/(cm² 24 h), again an approx. 95 times lower value compared to mouse skin, which is comparable to the former investigation (No. 3, table 2). With this experimental setup it was not possible to determine the flux of SPM7605 across human skin accurately. Due to a lack of capacity, no experiments with different supportive membranes were performed.

SPM8272 (OiBut/Fum; Fesoterodine) and SPM8224 (OiBut, free base of Fesoterodine)

The experiments with patches containing elther Fesoterodine or the free base of Fesoterodine were already reported [5,6]. While the passive transdermal delivery of Fesoterotine seemed to be not suitable, very high flux rates of the free base of Fesoterodine across human skin make SPM8224 a very promising candidate for the transdermal treatment of overactive bladder.

SPM7675 (DiBut, di-iso-bytyric acid ester)

SPM7675, the di-iso-butyric acid ester of SPM7605 (DiOH = active metabolite of Fesoterodine), is an oil with a purity of approx. 95%. Due to low amounts of drug available, a lack of capacity and generally lower permeation rates only five patch batches were prepared and investigated by means of drug permeation across hairless mouse skin. In accordance with the former data obtained for the racemic micture, permeation rates in the range of 120 to 150 µg/(cm² 24h) were observed (data not shown). Since these in vitro mouse skin data were not in the therapeutic range, no further studies with SPM7675 were performed.

SPM8302 (DiAc, di-acetic acid ester)

SPM8302, the di-acetic acid ester of SPM7605 (DiOH = active metabolite of Fesoterodine) is an oil with a purity of approx. 95%. More than 25 different lab scale patch batches were prepared (comp. Annex). The drug could be incorporated into the complete range of available pressure sensitive adhesives covering silicones, acrylates, ethylene vinyl acetate copolymers as well as styrene-block-copolymers (comp. Annex). Fig. 1 gives an example of the obtained flux rates across mouse skin.

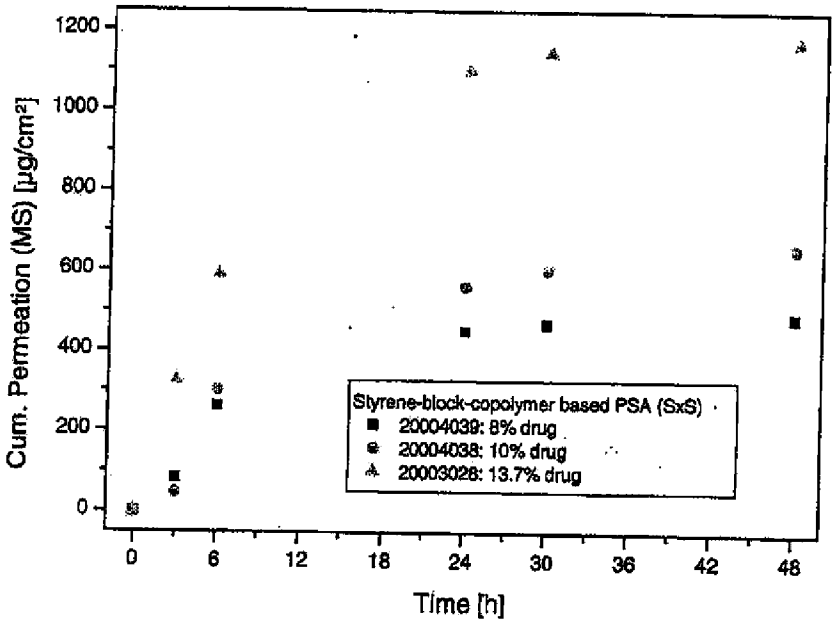


Fig. 1a: **Skin permeation across mouse skin** (calculated as release of active metabolite), batches prepared by lab scale hot melt processing by incorporating 8, 10 and 13.7% (w/w) SPM8302 into Dermagel 10127-113-3, a styrene-block-co-polymer based adhesive from National Starch & Chemical.

Very high flux rates, increasing with increasing drug loading, were observed (fig. 1a).

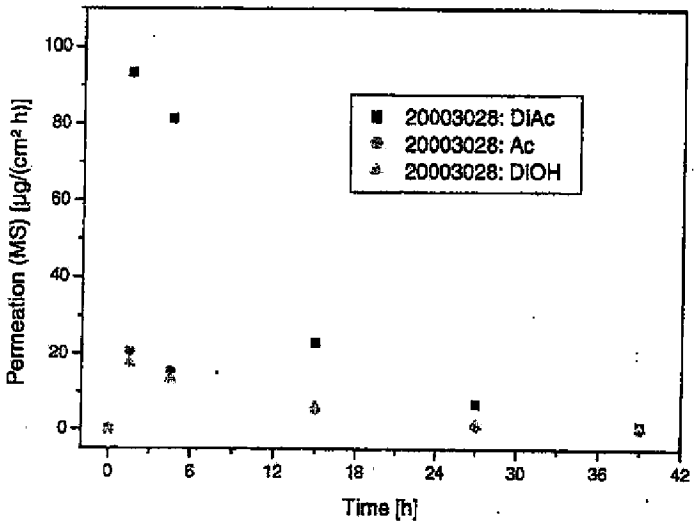


Fig. 1b: Differiential skin permeation as a function of different hydrolysis products

As outlined in fig. 1b initially ca. 20% of the drug were detected as monoester and additional 20% as active metabolite in the aceptor medium indicating the rapid hydrolysis of the prodrug once in contact with skin and/or water.

Two different samples were investigated in the LACDR human skin model. Fig. 2 outlines the initial permeation results which were in accordance with the former evaluation.

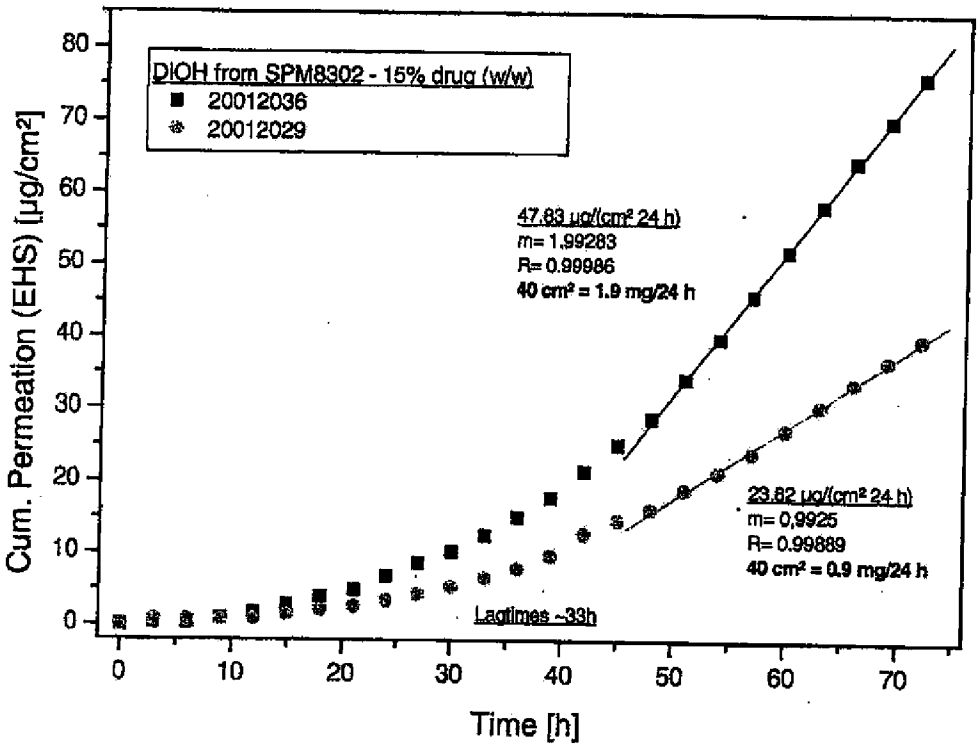


Fig. 2: Cumulative permeation across excised human skin (values corrected with the flux barrier of the supportive silastic sheeting), batches prepared by lab scale solvent coating (20012036: 15% (w/w) drug in acrylic type adhesive, National Starch & Chemical Duro Tak 387-4287) and hot melt processing (20012029: 15% (w/w) drug in silicone based adhesive (BioPSA, Dow Corning) plus additional inner phase polymer (10% (w/w) Vinapas = poly(viny acetate)))

Due to the very high permeation results across mouse skin, the flux rates across human skin seemed to be too low. Since always fresh human skin is used in the LACDR model, a likely explanation could be that remaining enzymatic activity in the skin led to fast drug hydrolysis and the generation of charged molecules. Unfortunately, the skin supporting silastic sheeting

is impermeable to charged molecules. This effect will of course only be visible in the experiment with the composite of human skin supported by the silastic sheeting, which explains, why always high permeation rates were found when testing the synthetic membrane alone.

An experimental change by replacing the supportive membrane with a dialysis membrane which is not impermeable to charge moleculaes, significantly improved the results as outlined in fig. 3.

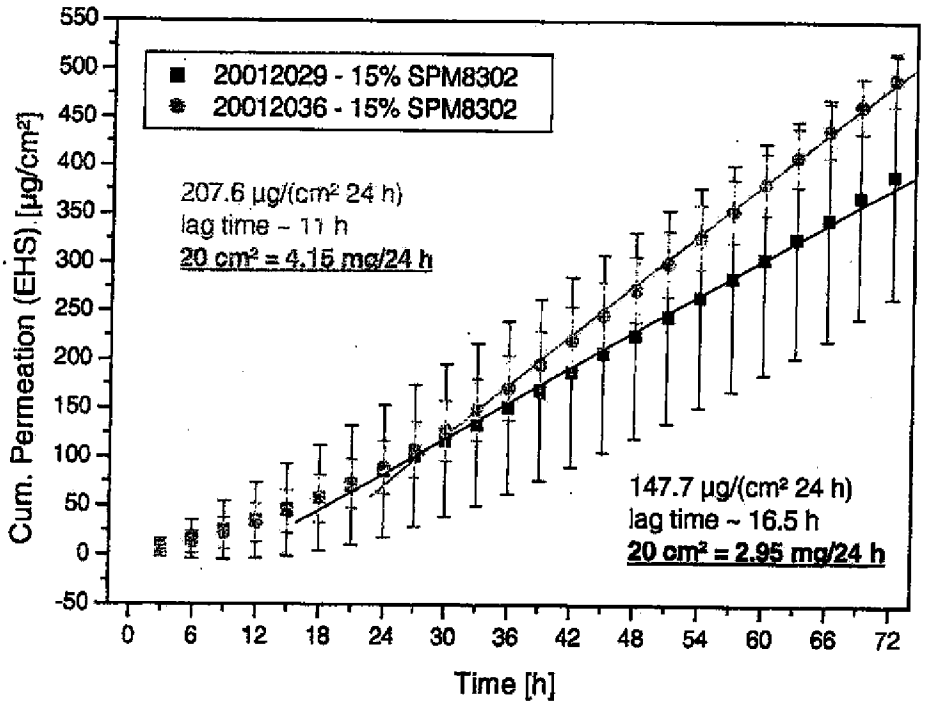


Fig. 3: Cumulative permeation across excised human skin (plus dialysis membrane, calculated as permeation of active metabolite)

Four to six times higher fux rates indicated that this experimental setup represented a more reasonable assessment of the flux across human skin. Moreover, the values found for batch 20012036 indicated the promising potential of SPM8302 to be used for the treatment of

overactive bladder. Patches with sizes in the range of 20 to 40 cm^2 could theoretically deliver 4 to 8 mg/24 h which is the current range of the oral Fesoterodine formulation.

CONCLUSIONS

After having already demonstrated the promising transdermal potential of SPM8224, the free base of Fesoterodine, here the alternative use of several different Fesoterodine related prodrugs from the SPM907 series was investigated.

Based on the results obtained, only SPM8302 could be used as alternative since its flux rates across human skin were found to be sufficient for the treatment of overactive bladder with patch sizes in the range of 20 to 40 cm^2 (equal to delivery of ca. 4 to 8 mg in 24 h). These data have to be confirmed in vivo.

ANNEX 1

Copies of the Certificates of Analysis
(signed originals stored at PH DOK)

SPM 8302	SPM 7605	SPM 8272	SPM 7675	SPM 8224
Ch.B.	Ch.B.	Ch.B.	Ch.B.	Ch.B.
20008079	20008039	20008042	20002029	20111080
20008078	20008038	20008041	20002032	20111085
20008060	20008037	20008040	20002030	20111086
20008059	20008036	20004054	20002027	20111087
20008057	20008032	20004053	20002021	20111095
20008056	20008031	20003034		20201027
20008055	20008030	20002052		20201028
20008033	20008029	20002051		
20006011	20106045	20002050		
20006010	20106043	20002046		
20006009		20002042		
20004058		20002041		
20004057		20002040		
20004056		20002037		
20004055		20002031		
20004041		20002020		
20004040		20002019		
20004039		20002018		
20004038		20104034		
20003052		20104035		
20003051		20104037		
20003050		20104038		
20003033		20106061		
20003032				
20003031				
20003030				
20003029				
20003028				
20002036				
20002035				
20002033				
20012010				
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20012019				
20012024				
20012025				
20012026				
20012027				
20012028				
20012029				
20012030				
20012036				

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ 002
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN004A-M	Analysendatum :	06.-09.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 8 Wochen TK-Schrank SKH-1o
1=160µm R ; 2=146µm R 34,3 ; 3=147µm R ,4=149µm R 30,7g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	di-OH-Base						
[h]	1	2	3	4	MW	SD	add.
3	518,7	326,5	306,7	686,2	459,5	178,8	459,5
6	753,0	549,2	483,2	648,5	608,4	117,9	1068,0
24	2868,5	2501,4	2287,0	2634,6	2572,9	243,6	3640,9
30	778,9	685,1	677,4	742,6	721,0	48,3	4361,8
48	1641,8	1542,4	1593,5	1524,1	1575,4	53,1	5937,3
54	421,0	429,9	457,6	385,8	423,5	29,6	6360,8
72	896,7	1013,1	1153,2	851,3	978,6	134,9	7339,4

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	971,5	µg
Regressionskoeffizient (m) =	2,3	µg/h
Korrelationskoeffizient (r) =	0,0744	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ003
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN006A-F	Analysendatum :	13.-17.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 1 Woche TK-Schrank SKH-1♂
1=117µm R ; 2=115µm ; 3=124µm R ,4=113µm R 33,4g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert
Zusammensetzung : SPM 7502 ; SPM 7504 ; SPM 7500

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM 7502						SPM 7504		SPM 7500		Summe	
[h]	1	2	3	4	MW	SD	MW	SD	MW	SD	MW	kumu.
3	41,3	63,8	55,1	77,3	59,4	15,1	75,3	8,4	15,3	1,4	[illegible]	149,9
6	128,8	141,2	143,3	162,9	144,0	14,1	75,3	10,6	10,4	0,7	229,7	379,7
24	638,5	47,2	576,7	754,6	504,2	313,5	336,7	81,5	68,8	32,5	909,8	1289,5
30	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	8,5	0,9	8,5	1297,9
48	603,9	828,4	654,7	676,6	690,9	96,6	115,4	16,0	49,5	5,5	855,8	2153,7
54	198,0	231,0	223,8	218,6	217,8	14,2	30,0	9,3	11,2	1,7	259,1	2412,8
72	515,7	566,3	559,5	559,4	550,2	23,2	66,4	6,1	39,8	4,0	656,5	3069,2

MW = Mittelwert SD = Standardabweichung MW = Mittelwert SD = Standardabweichu

Achsenabschnitt (b)= 244,6 µg
Regressionskoeffizient (m 5,7 µg/h
Korrelationskoeffizient (r) 0,4029

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ005
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN008A-F	Analysendatum :	13.-17.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 1 Woche TK-Schrank SKH-1♂
1=109µm R ; 2=116µm ;R 26,9 ; 3=147µm R ,4=136µm R 25,1g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert
Zusammensetzung : SPM 7504 ; SPM 7500

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM 7504						SPM 7500		Summe	
[h]	1	2	3	4	MW	SD	MW	SD	MW	kumu.
3	506,3	587,1	692,3	374,7	540,1	134,0	29,8	5,4	569,8	569,8
6	617,1	621,9	654,8	472,7	591,6	81,0	24,6	2,0	616,2	1186,1
24	2244,7	2178,9	2340,2	2040,9	2201,2	125,7	125,6	10,4	2326,7	3512,8
30	499,6	520,7	500,9	510,6	507,9	9,8	30,2	2,6	538,1	4051,0
48	948,9	1058,0	911,8	1027,1	986,5	67,7	89,4	10,0	1075,8	5126,8
54	231,8	288,4	213,7	271,2	251,3	34,5	24,2	3,0	275,5	5402,3
72	476,0	675,3	414,7	591,3	539,3	116,5	50,6	7,7	589,9	5992,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	999,2	µg
Regressionskoeffizient (m) =	-4,2	µg/h
Korrelationskoeffizient (r) =	-0,1562	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ 011
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN031A-C	Analysendatum :	04.12.98
ABV vom :	analog OBU 0469.100		

Bemerkungen: 10 Wochen lebend 5 Wochen TK-Schrank SKH-1♂
1=130µm R ; 2=128µm R 32,1 ; 3=149µm R ,4=154µm R 31,8g
Die Proben wurden nicht aufkonzentriert und nicht filtriert

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM_7501						SPM_7500 zu SPM_7501		MW
[h]	1	2	3	4	MW	SD	MW	SD	add.
3	363	582	237	624	**452**	**183**	**25**	**7**	**476**
6	765	1046	615	1235	**915**	**278**	**43**	**9**	**959**
24	2240	2658	2106	3086	**2523**	**443**	**189**	**21**	**2711**
30	2638	3065	2531	3539	**2943**	**459**	**212**	**21**	**3155**
48	2857	3277	2770	3768	**3168**	**457**	**295**	**19**	**3463**
54	3200	3564	3124	4014	**3476**	**407**	**327**	**18**	**3802**
72	3721	3989	3635	4317	**3916**	**307**	**386**	**17**	**4302**

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	848,3	µg
Regressionskoeffizient (m) =	48,3	µg/h
Korrelationskoeffizient (r) =	0,9403	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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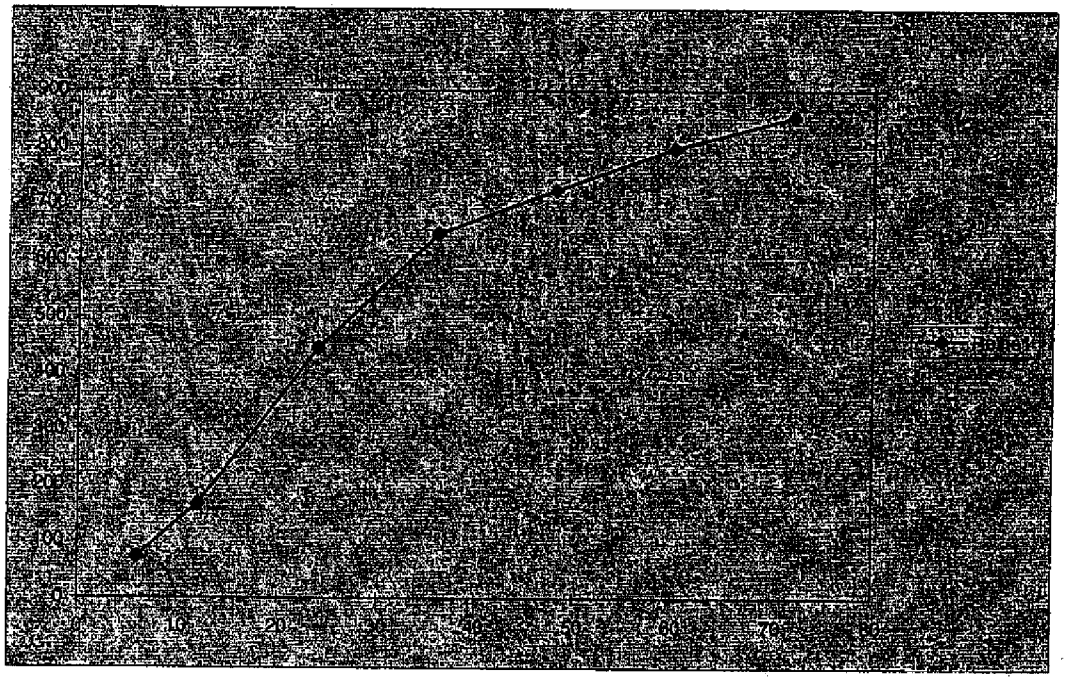
Auswertung Wirkstoff SPM 7500

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**0,00**	0,00	0,00	**0,00**
12	**0,00**	0,00	0,00	**0,00**
24	**0,00**	0,00	0,00	**0,00**
36	**0,00**	0,00	0,00	**0,00**
48	**2,39**	0,51	21,41	**2,39**
60	**3,04**	0,70	23,09	**5,43**
72	**2,85**	2,24	78,81	**8,27**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**72,52**	0,00	0,00	**72,52**	0,00	0,00
12	**93,11**	0,00	0,00	**165,63**	0,00	0,00
24	**279,19**	0,00	0,00	**444,82**	0,00	0,00
36	**200,90**	0,00	0,00	**645,72**	0,00	0,00
48	**76,57**	0,00	0,00	**722,28**	0,00	0,00
60	**74,45**	0,00	0,00	**796,73**	0,00	0,00
72	**56,92**	0,00	0,00	**853,65**	0,00	0,00



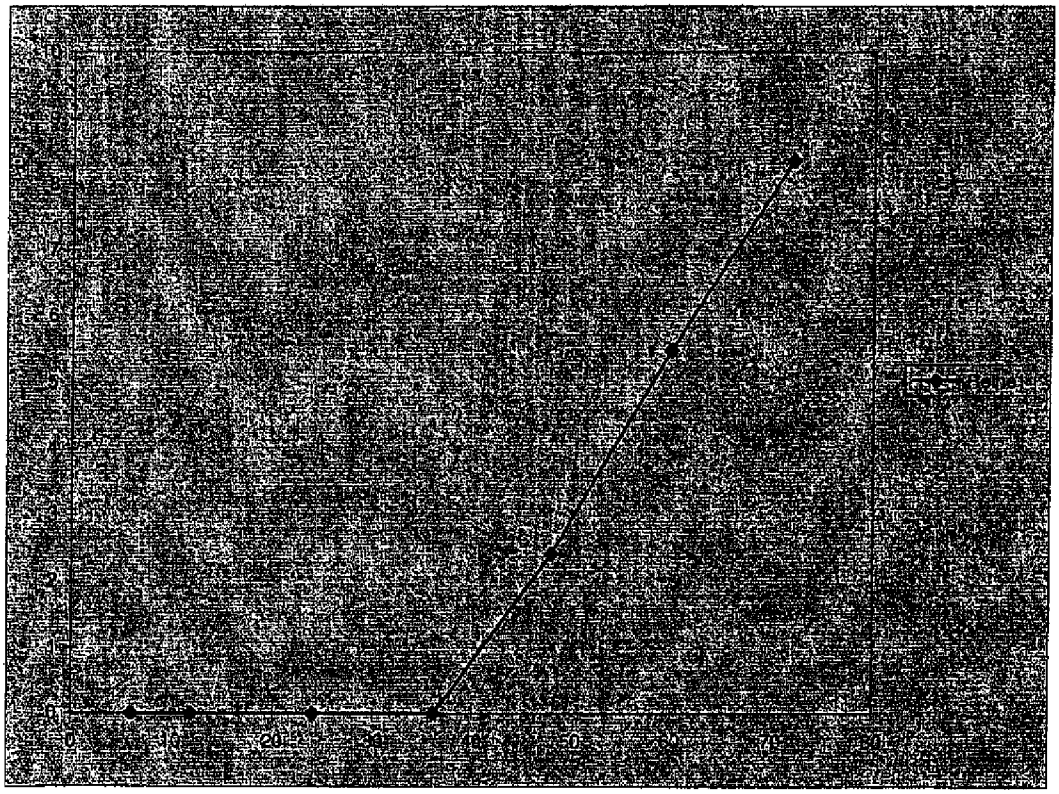
für SIL kumuliert
linearer Bereich von 6-24 h
lineare Regression

r^2	0,994665	
m	19,65	[µg/cm²*h]
b	-51,03	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 117,91

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 235,82

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	0,00	0,00
36	0,00	0,00
48	2,41	2,41
60	3,08	5,49
72	2,88	8,37



Hautpermeation des Wirkstoffs SPM 9080

linearer Bereich von 48-72h

lineare Regression

r^2	0,999632	
m	0,25	[µg/cm²*h]
b	-9,47	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 9080 über 24 h von:

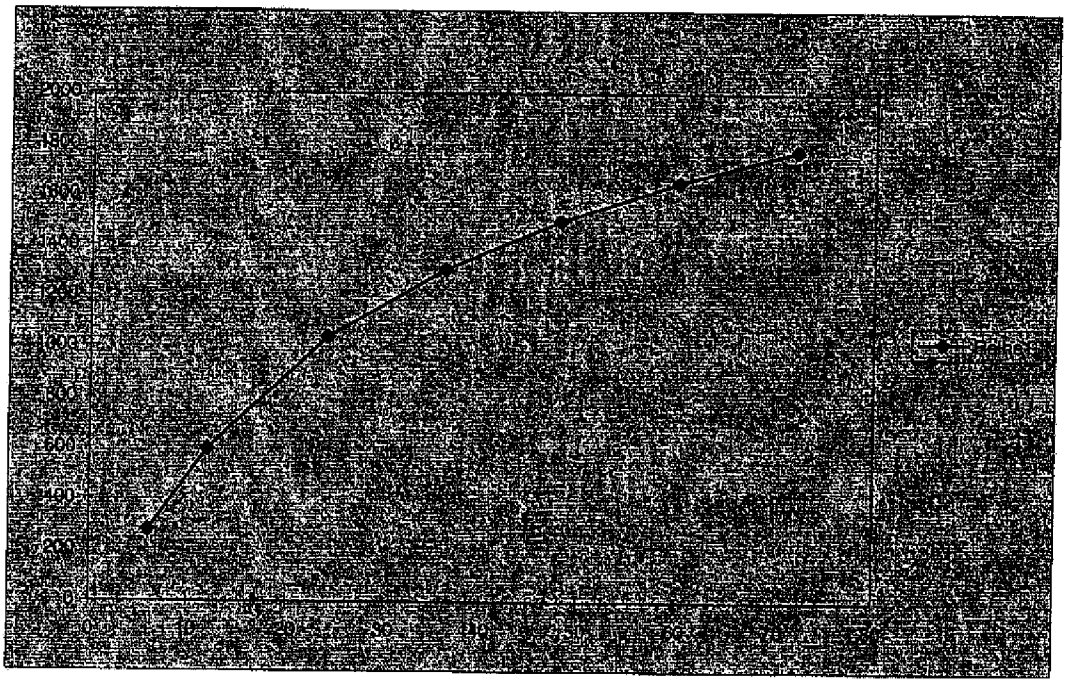
5,96 µg/cm² 24 h

lag-time: **38,1 h**

Auswertung Wirkstoff SPM 7502

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**2,30**	0,00	0,00	**2,30**
12	**7,04**	0,00	0,00	**9,34**
24	**25,23**	0,00	0,00	**34,57**
36	**31,47**	0,00	0,00	**66,04**
48	**31,07**	0,00	0,00	**97,11**
60	**30,40**	0,00	0,00	**127,50**
72	**27,08**	0,00	0,00	**154,58**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**276,75**	66,89	24,17	**276,75**	66,89	24,17
12	**320,76**	32,52	10,14	**597,51**	99,41	16,64
24	**440,59**	26,58	6,03	**1038,09**	72,83	7,02
36	**268,02**	8,75	3,26	**1306,12**	81,58	6,25
48	**192,03**	35,40	18,44	**1498,15**	46,17	3,08
60	**153,48**	19,27	12,56	**1651,64**	26,90	1,63
72	**126,51**	7,68	6,07	**1778,14**	19,22	1,08



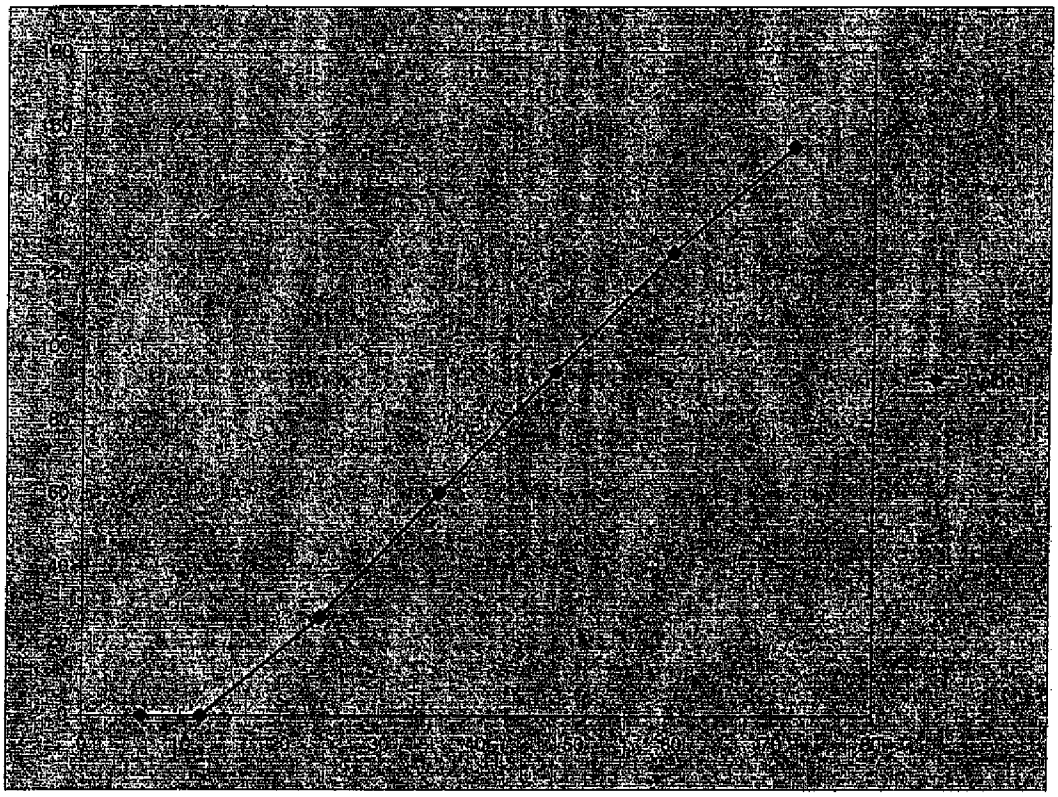
für SIL kumuliert
linearer Bereich von 6-72 h
lineare Regression

r^2	0,931582	
m	41,50	[µg/cm²*h]
b	56,46	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 249,00

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 497,99

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	26,58	26,58
36	33,59	60,17
48	33,14	93,31
60	32,37	125,68
72	28,63	154,32



Hautpermeation des Wirkstoffs SPM 7502

linearer Bereich von 24-72h

lineare Regression

r^2	0,999095	
m	2,67	[µg/cm²*h]
b	-36,38	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7502 über 24 h von:

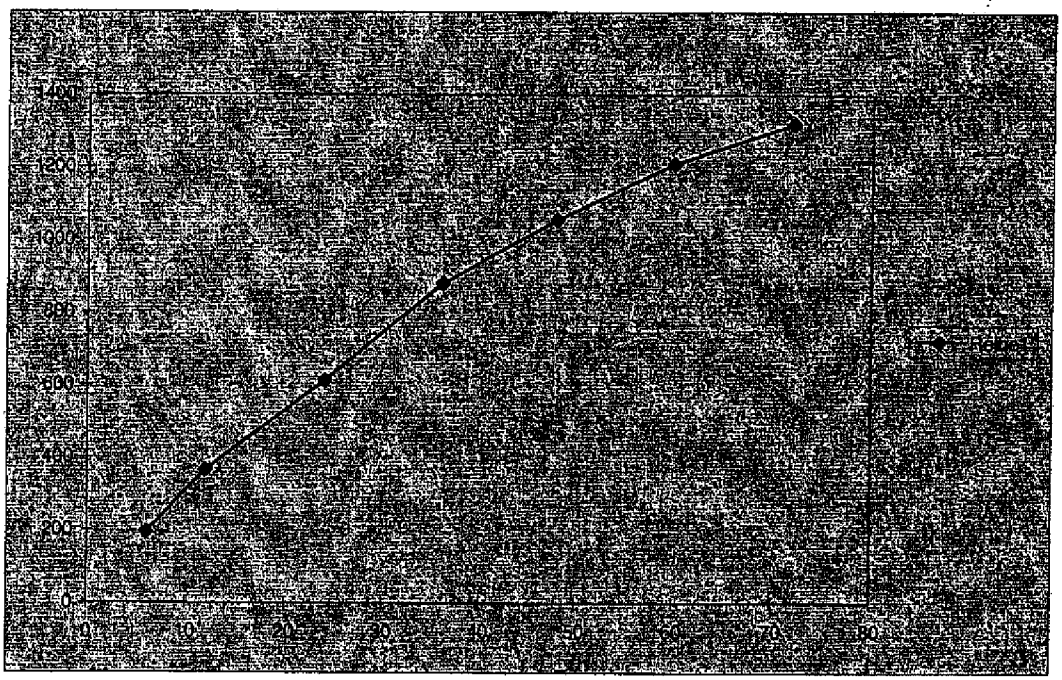
64,20 µg/cm²*24 h

lag-time: **13,6 h**

Auswertung Wirkstoff SPM 7504

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**0,00**	0,00	0,00	**0,00**
12	**0,00**	0,00	0,00	**0,00**
24	**3,73**	0,00	0,00	**3,73**
36	**8,73**	0,00	0,00	**12,46**
48	**7,16**	0,00	0,00	**19,62**
60	**4,22**	0,00	0,00	**23,84**
72	**6,77**	0,00	0,00	**30,62**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**195,02**	80,08	41,06	**195,02**	80,08	41,06
12	**170,12**	53,21	31,28	**365,13**	133,30	36,51
24	**248,29**	68,26	27,49	**613,43**	201,56	32,86
36	**267,65**	82,65	30,88	**881,08**	284,21	32,26
48	**174,81**	11,33	6,48	**1055,89**	295,54	27,99
60	**154,31**	28,40	18,40	**1210,19**	323,94	26,77
72	**109,97**	66,64	60,59	**1320,17**	390,58	29,59



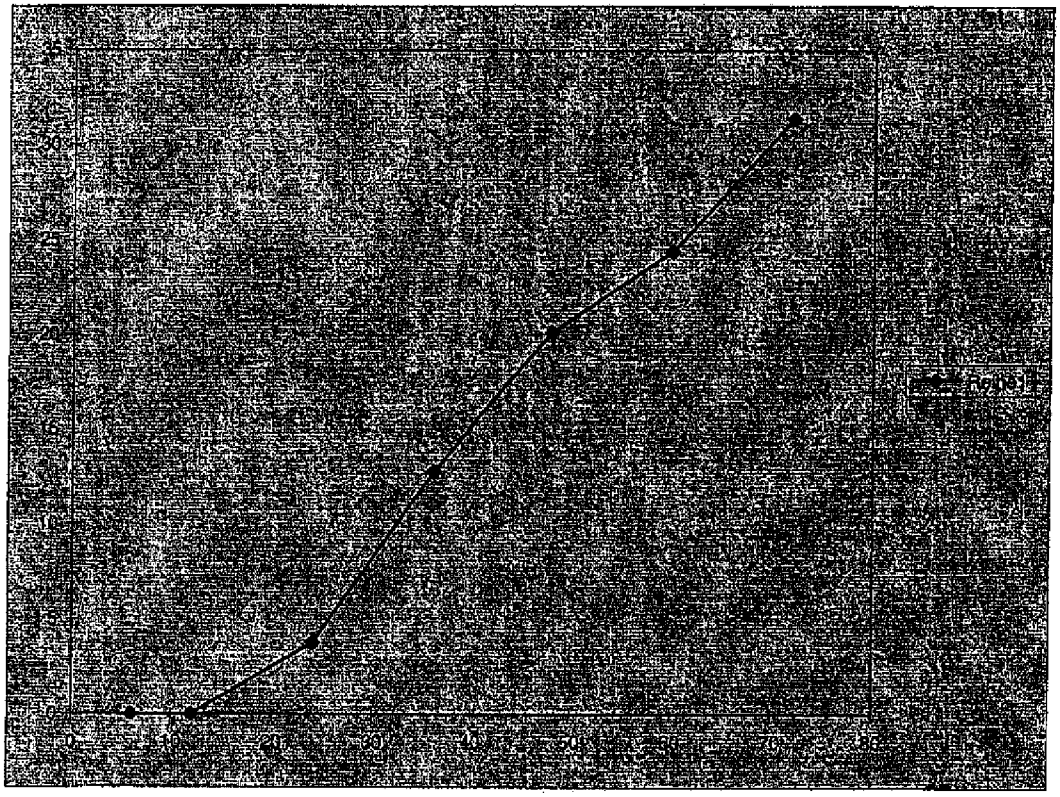
für SIL kumuliert
linearer Bereich von 6-72 h
lineare Regression

r^2	0,975393	
m	22,88	[µg/cm²*h]
b	70,87	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 137,28

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 274,56

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	3,79	3,79
36	9,01	12,80
48	7,35	20,15
60	4,29	24,44
72	6,94	31,38



Hautpermeation des Wirkstoffs SPM 7504

linearer Bereich von 24-72h

lineare Regression

r^2	0,986107	
m	0,56	[µg/cm²*h]
b	-8,22	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7504 über 24 h von:

13,37 µg/cm²*24 h

lag-time: **14,8 h**

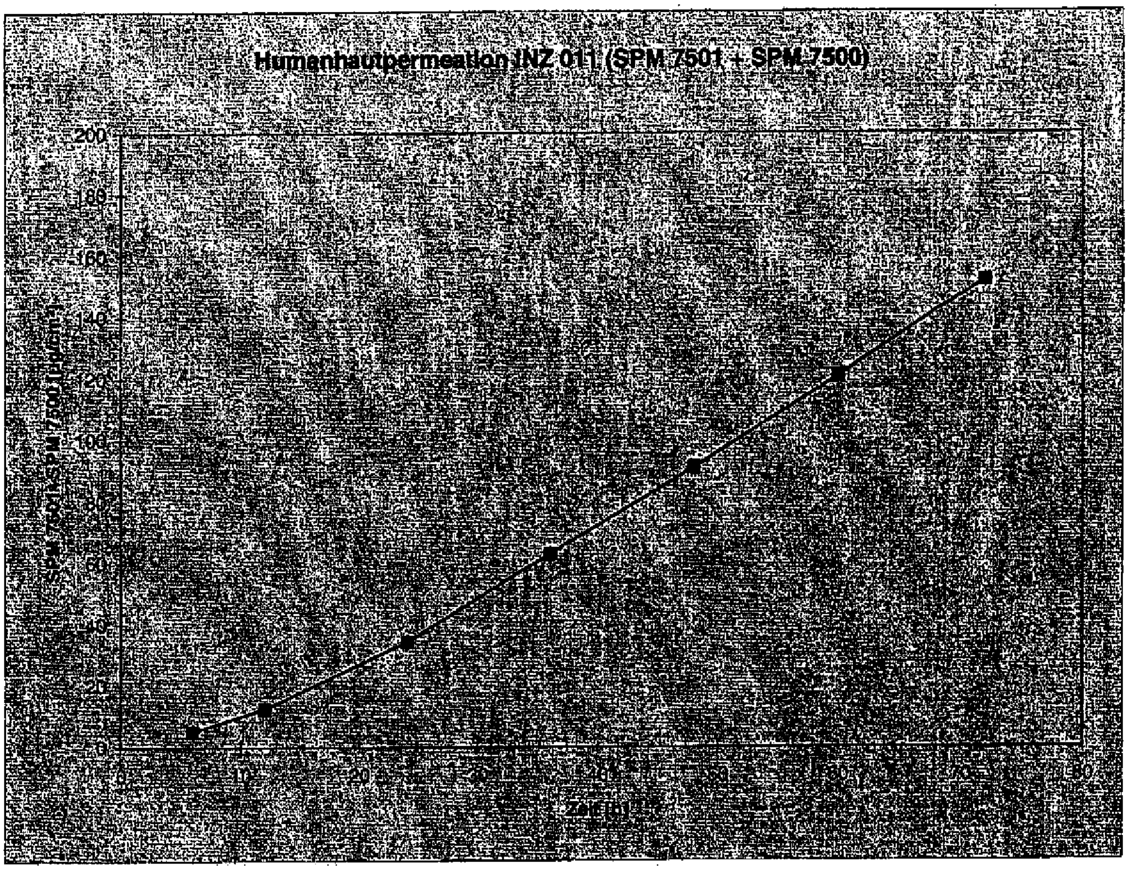
	Wirkstoff SPM 7501		Metabolit SPM 7500	
Zeit [h]	Haut mean	Haut kumuliert mean	Haut mean	Haut kumuliert mean
6	3,82	3,82	1,07	1,07
12	6,30	10,12	0,83	1,90
24	20,00	30,11	1,54	3,43
36	26,57	56,69	1,69	5,12
48	25,52	82,21	2,01	7,13
60	27,13	109,33	1,94	9,07
72	29,24	138,57	1,83	10,90

Metabolit SPM 7500
umgerechnet in Wirkstoff SPM 7501

Zeit [h]	Haut mean	Haut kumuliert mean
6	1,33	1,33
12	1,03	2,36
24	1,92	4,28
36	2,11	6,39
48	2,51	8,89
60	2,41	11,30
72	2,28	13,58

Summe aus Wirkstoff SPM 7501 und Metabolit 7500

Zeit [h]	Haut mean	Haut kumuliert mean
6	**5,15**	**5,15**
12	**7,33**	**12,48**
24	**21,91**	**34,39**
36	**28,68**	**63,07**
48	**28,03**	**91,10**
60	**29,54**	**120,64**
72	**31,52**	**152,15**



Hautpermeation von SPM 7501 + SPM 7500

linearer Bereich von 24-72 h

r^2	0,999484959	
m	2,442	[µg/cm²*h]
b	-24,964	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7501 + SPM 7500 über 24 h von:

58,6 µg/cm²/24 h

lag-time **10,2 h**

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM7605**	Ch.-B.:	20008029
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IB0773_MHP	Analysendatum :	17.08.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=170; 2=162 3=164, 30,3g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

mg DIOH / 5cm²					
Zeit [h]	1	2	3	**MW**	SD
3	0,34	0,17	0,28	**0,26**	0,09
6	0,64	0,44	0,56	**0,55**	0,10
24	1,60	1,53	1,56	**1,56**	0,04
30	1,83	1,78	1,81	**1,81**	0,02
48	2,27	2,30	2,34	**2,30**	0,03

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,28	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,98122	

$Q \approx t$ $Q = t \cdot m + b$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM7605**	Ch.-B.:	20008030
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IB0773_MHP	Analysendatum :	17.08.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=148µm; 2=154µm 3=165µm, 30,1g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VTWasser 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,24	0,36	0,39	0,33	0,08
6	0,34	0,42	0,45	0,40	0,06
24	1,46	1,52	1,56	1,51	0,05
30	1,75	1,80	1,84	1,79	0,05
48	2,33	2,38	2,43	2,38	0,05

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,22	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,98876	

$Q = t$ $Q = t \cdot m + b$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat : **SPM 907 TDS**
SPM 7605
Ch.-B.: 20106045
TDS- Fläche : 5 cm²
Sollgehalt : 15%
Analysen-Nr: 20106043_6044_6045_6061_AA_MHP_01 + 02
Analysendatum : 09.07.2001
ABV vom : analog OBU 0469.10

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=160µm; 2=168µm 3=148µm, 34,7g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
Ausgangsanalyse

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	**MW**	SD
3	0,09	0,09	0,09	**0,09**	0,00
6	0,35	0,36	0,43	**0,38**	0,05
24	1,16	1,16	1,21	**1,18**	0,03
30	1,36	1,35	1,39	**1,37**	0,02
48	1,83	1,77	1,83	**1,81**	0,04

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,12	mg
Regressionskoeffizient (m) =	0,04	mg/h
Korrelationskoeffizient (r) =	0,98181	

$Q = t$ $Q = t \cdot m + b$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIII

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	**SPM 907 TDS**
	SPM 7605
Ch.-B.:	20106043
TDS- Fläche :	5 cm^2
Sollgehalt :	15%
Analysen-Nr:	20106043_6044_6045_6061_AA_MHP_01 + 02
Analysendatum :	09.07.2001
ABV vom :	analog OBU 0469.10

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=174µm; 2=179µm 3=168µm, 31,7g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
Ausgangsanalyse

Tabelle der kumulierten Freisetzung in mg / 5 cm^2

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,07	0,27	0,08	**0,14**	0,11
6	0,38	0,76	0,37	**0,50**	0,22
24	1,59	2,45	1,47	**1,84**	0,54
30	1,98	2,94	1,82	**2,25**	0,61
48	3,00	4,10	2,63	**3,24**	0,77

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,07	mg
Regressionskoeffizient (m) =	0,07	mg/h
Korrelationskoeffizient (r) =	0,99521	

$Q \approx t$ $Q = t \cdot m + b$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

Diffusion experiment with SPM 907 patches on silastic sheeting

Purpose of the study:

To investigate the influence of four formulations on the release rate of SPM 907 patches. The present study has been performed without skin in the cells in order to measure the initial release rate of active ingredient from the formulations through the used membrane. The four following experiments will be performed with skin from four different donors.

Patch:

Active ingredient: SPM 907
Batch numbers: 20012029, 20012036, 20106043 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Diffusion experiment:

Date: 7 to 10 Sept. 2001

Used cells:
diffusion cells with spiral groove (n=8); groove area: 0.552 cm^2.

Separator between acceptor phase and skin/patch:
Silicone sheeting (Silastic sheeting), implant grade elastomer non sterile, non-reinforced;
Manufacturer: Nagor limited, P.O. Box 21, Douglas, Island of Man
Cat. nr. NA 500-1, Thickness 0.125 mm, Lot nr. 11603/1
No special pretreatment, other than cleaning, applied.

Diameter of separator and patch punch-outs: 1.8 cm.

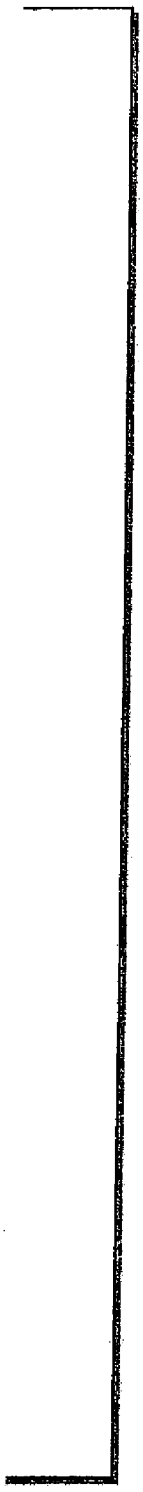
Setup diffusion cells:

Cell nr.	Batch
1 & 2	20012029
3 & 4	20012036
5 & 6	20106043
7 & 8	20106061

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 32.0 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

Some sample from cell 5 was lost at 69 and 72 hours due to a tilted tube holder in the fraction collector. Use a higher volume for the corresponding fractionsfor calculations (see Volume fractions tab).



Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,010 g/ml

Faktor zur Umrechnung auf cm²: 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes (g) full	fractions (ml)	8272 µg/ml	8272 µg/fraction	Fraction *F=1,812	Fraction Mittelwert	DIOH µg/ml	DIOH µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert	Diacetat µg/ml	Diacetat µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert
3	1	17,152	33,385	16,074					0,44	7,073	12,815		17,44	280,328	507,955	
	2	16,972	32,800	15,673					0,45	7,053	12,780	12,798	16,44	257,661	466,883	487,419
	3	17,146	33,037	15,735					0,42	6,609	11,975		18,30	287,955	521,774	
	4	16,884	32,889	15,848					0,73	11,569	20,963	16,469	22,20	351,828	637,512	579,643
	5	17,191	33,293	15,944					0,39	6,218	11,267					
	6	17,144	32,870	15,572					0,25	3,893	7,054	9,161				
	7	17,129	32,663	15,382	0,30	4,615	8,362		0,11	1,692	3,068					
	8	16,997	32,554	15,404	0,33	5,083	9,211	8,786	0,11	1,694	3,070	3,068				
6	1	16,790	33,002	16,053					0,34	5,458	9,890		14,49	232,609	421,488	
	2	17,018	32,890	15,716					0,48	7,544	13,670	11,780	14,54	228,617	414,072	417,780
	3	16,932	32,670	15,782					0,38	5,997	10,867		14,5	228,836	414,650	
	4	17,137	33,168	15,874					0,54	8,572	15,532	18,199	16,48	261,601	474,021	444,336
	5	17,140	33,322	16,023					1,02	16,344	29,615					
	6	17,215	33,036	15,666					0,86	13,473	24,412	27,014				
	7	16,946	32,586	15,487	0,49	7,59	13,750		0,15	2,323	4,209					
	8	17,071	32,807	15,582	0,44	6,86	12,423	13,087	0,12	1,870	3,388	3,799				
9	1	17,177	33,387	16,051					0,3	4,82	8,725		10,18	163,40	296,081	
	2	17,100	32,962	15,707					0,38	5,97	10,815	9,770	10,36	162,72	294,848	295,464
	3	17,125	33,070	15,789					0,27	4,26	7,724		11,23	177,31	321,280	
	4	17,180	33,187	15,880					0,32	5,08	9,208	8,466	12,62	200,40	363,130	342,205
	5	16,994	33,152	16,000					0,86	13,76	24,933					
	6	16,963	32,736	15,618					0,77	12,03	21,791	23,362				
	7	17,074	32,691	15,464	0,37	5,72	10,368		0,13	2,01	3,643					
	8	17,217	32,949	15,578	0,32	4,98	9,033	9,700	0,1	1,56	2,823	3,233				
12	1	17,202	33,391	16,030					0,27	4,33	7,843		7,65	122,63	222,209	
	2	16,912	32,768	15,701					0,27	4,24	7,681	7,762	7,74	121,62	220,199	221,204
	3	17,114	33,033	15,763					0,33	5,20	9,426		8,88	139,97	253,635	
	4	17,089	33,104	15,858					0,35	5,55	10,057	9,741	9,82	155,73	282,176	267,905
	5	17,143	33,302	16,001					0,72	11,52	20,875					
	6	17,146	32,922	15,621					0,63	9,84	17,833	19,354				
	7	17,192	32,846	15,501	0,25	3,88	7,022		0,1	1,55	2,809					
	8	17,224	32,937	15,559	0,23	3,58	6,484	6,753	0,08	1,24	2,255	2,532				

15	1	17,338	33,503	16,007					0,16	2,56	4,641		6,09	97,48	176,633		
	2	16,941	32,787	15,691					0,18	2,82	5,118	4,879	6,06	94,93	172,010	174,322	
	3	17,152	33,062	15,774					0,24	3,79	6,860		7,40	116,73	211,508		
	4	17,031	33,043	15,855					0,18	2,85	5,171	6,016	8,26	130,96	237,304	224,406	
	5	17,156	33,304	15,990					0,63	10,07	18,253						
	6	17,126	32,889	15,608					0,55	8,58	15,555	16,904					
	7	17,141	32,723	15,429	0,16	2,47	4,473		0,08	1,23	2,237						
	8	17,204	32,906	15,548	0,16	2,49	4,508	4,490	0,07	1,09	1,972	2,104					
18	1	17,058	33,216	16,000					0,17	2,72	4,929		5,01	80,16	145,246		
	2	17,180	32,996	15,661					0,13	2,04	3,689	4,309	5,00	78,30	141,888	143,567	
	3	17,159	33,061	15,746					0,23	3,62	6,562		6,80	107,07	194,017		
	4	17,142	33,135	15,836					0,18	2,85	5,165	5,864	6,19	98,03	177,623	185,820	
	5	17,253	33,387	15,976					0,53	8,47	15,343						
	6	17,180	32,932	15,598					0,48	7,49	13,566	14,454					
	7	17,130	32,740	15,457	0,12	1,85	3,361		0,06	0,93	1,680						
	8	17,201	32,906	15,551	0,13	2,02	3,663	3,512	0,06	0,93	1,891	1,686					
21	1	17,062	33,160	15,960					0,13	2,07	3,760		4,32	68,95	124,932		
	2	16,977	32,775	15,643					0,11	1,72	3,118	3,439	4,30	67,27	121,885	123,409	
	3	16,944	32,827	15,727					0,19	2,99	5,415		5,22	82,10	148,759		
	4	17,145	33,102	15,801					0,21	3,32	6,012	5,714	5,81	91,80	166,344	157,551	
	5	17,130	33,244	15,956					0,44	7,02	12,721						
	6	17,229	32,962	15,579					0,42	6,54	11,856	12,289					
	7	17,187	32,789	15,449	0,09	1,39	2,519		0,05	0,77	1,400						
	8	17,253	32,922	15,515	0,10	1,55	2,811	2,665	0,05	0,78	1,406	1,403					
24	1	17,048	33,153	15,947					0,11	1,75	3,179		3,76	59,96	108,650		
	2	17,157	32,956	15,644					0,14	2,19	3,969	3,574	3,71	58,04	105,168	106,909	
	3	17,021	32,881	15,705					0,18	2,83	5,122		4,47	70,20	127,201		
	4	17,088	33,032	15,788					0,2	3,16	5,721	5,422	5,05	79,73	144,467	135,834	
	5	17,192	33,301	15,951					0,37	5,90	10,694						
	6	17,149	32,839	15,536					0,37	5,75	10,416	10,555					
	7	17,099	32,662	15,410	0,07	1,08	1,955		0,04	0,62	1,117						
	8	17,042	32,683	15,488	0,08	1,24	2,245	2,100	0,03	0,46	0,842	0,979					

27	1	17,160	33,256	15,938					0,15	2,39	4,332		3,25	51,80	93,860	
	2	16,898	32,657	15,605					0,12	1,87	3,393	3,863	3,29	51,34	93,026	93,443
	3	17,190	33,069	15,723					0,13	2,04	3,704		3,96	62,26	112,823	
	4	17,044	32,981	15,781					0,17	2,68	4,861	4,282	4,41	69,59	126,103	119,463
	5	16,967	33,041	15,916					0,32	5,09	9,229					
	6	16,960	32,652	15,538					0,32	4,97	9,010	9,119				
	7	17,200	32,750	15,398	0,06	0,92	1,674		0,04	0,62	1,116					
	8	17,058	32,679	15,468	0,06	0,93	1,682	1,678	0,03	0,46	0,841	0,978				
30	1	17,166	33,255	15,931					0,08	1,27	2,309		2,97	47,32	85,736	
	2	17,179	32,950	15,616					0,09	1,41	2,547	2,428	2,91	45,44	82,344	84,040
	3	17,301	33,134	15,678					0,15	2,35	4,261		3,46	54,25	98,292	
	4	17,049	32,984	15,779					0,16	2,52	4,575	4,416	3,91	61,70	111,791	105,042
	5	17,158	33,243	15,927					0,27	4,30	7,792					
	6	17,106	32,814	15,554					0,26	4,04	7,328	7,560				
	7	17,285	32,852	15,414	0,05	0,77	1,397		0,03	0,46	0,838					
	8	17,129	32,736	15,454	0,05	0,77	1,400	1,398	0,02	0,31	0,560	0,699				
33	1	17,090	33,169	15,921					0,11	1,75	3,173		2,63	41,87	75,874	
	2	17,135	32,891	15,602					0,11	1,72	3,110	3,142	2,62	40,88	74,067	74,971
	3	17,162	33,026	15,706					0,12	1,89	3,416		3,11	48,65	88,522	
	4	17,027	32,953	15,770					0,16	2,52	4,572	3,994	3,49	55,04	99,727	94,125
	5	17,207	33,300	15,935					0,22	3,51	6,352					
	6	17,032	32,704	15,518					0,21	3,26	5,905	6,129				
	7	17,116	32,677	15,408	0,04	0,62	1,117		0,03	0,46	0,838					
	8	17,167	32,780	15,460	0,04	0,62	1,121	1,119	0,02	0,31	0,560	0,699				
36	1	17,015	33,086	15,913					0,1	1,59	2,884		2,02	32,15	58,247	
	2	17,323	33,093	15,615					0,09	1,41	2,547	2,715	2,10	32,79	59,420	58,833
	3	17,024	32,893	15,713					0,13	2,04	3,701		2,41	37,67	68,619	
	4	17,131	33,044	15,757					0,14	2,21	3,997	3,849	2,74	43,17	78,232	73,425
	5	17,142	33,219	15,919					0,2	3,18	5,769					
	6	17,166	32,865	15,545					0,18	2,80	5,070	5,420				
	7	16,871	32,428	15,404	0,04	0,62	1,117		0,03	0,46	0,837					
	8	16,963	32,568	15,452	0,04	0,62	1,120	1,118	0,02	0,31	0,560	0,699				

39	1	17,202	33,239	15,880					0,13	2,06	3,741		2,02	32,08	58,124	
	2	17,182	32,896	15,560					0,15	2,33	4,229	3,985	2,10	32,68	59,209	58,666
	3	17,019	32,828	15,654					0,14	2,19	3,971		2,41	37,73	68,360	
	4	17,234	33,135	15,745					0,16	2,52	4,565	4,268	2,74	43,14	78,173	73,266
	5	17,273	33,314	15,884					0,17	2,70	4,893					
	6	17,110	32,773	15,509					0,14	2,17	3,934	4,414				
	7	17,102	32,627	15,373	0,03	0,46	0,836		0,05	0,77	1,393					
	8	17,151	32,718	15,414	0,03	0,46	0,838	0,837	0,02	0,31	0,559	0,976				
42	1	16,781	32,820	15,882					0,12	1,91	3,453		1,81	28,75	52,088	
	2	17,124	32,853	15,575					0,12	1,87	3,387	3,420	1,93	30,06	54,468	53,278
	3	16,957	32,794	15,662					0,14	2,20	3,978		2,14	33,56	60,809	
	4	17,049	32,937	15,792					0,15	2,36	4,276	4,127	2,46	38,70	70,127	65,468
	5	17,281	33,334	15,896					0,15	2,38	4,320					
	6	17,168	32,840	15,518					0,12	1,86	3,374	3,847				
	7	17,056	32,563	15,355	0,03	0,46	0,835		0,02	0,31	0,556					
	8	17,056	32,637	15,428	0,03	0,46	0,839	0,837	0,02	0,31	0,559	0,558				
45	1	17,412	33,449	15,880					0,18	2,86	5,179		1,76	27,95	50,643	
	2	16,824	32,546	15,568					0,14	2,18	3,949	4,564	1,74	27,09	49,084	49,863
	3	17,072	32,898	15,671					0,13	2,04	3,691		1,88	29,46	53,384	
	4	17,122	33,024	15,746					0,15	2,36	4,280	3,986	2,15	33,85	61,344	57,364
	5	17,233	33,294	15,904					0,13	2,07	3,746					
	6	17,308	32,963	15,502					0,12	1,96	3,371	3,558				
	7	17,105	32,651	15,394	0,03	0,46	0,837		0,03	0,46	0,837					
	8	16,777	32,338	15,408	0,03	0,46	0,836	0,837	0,02	0,31	0,558	0,698				
48	1	17,169	33,192	15,866					0,12	1,90	3,450		1,62	25,70	46,573	
	2	17,140	32,865	15,571					0,11	1,71	3,104	3,277	1,57	24,45	44,297	45,435
	3	17,055	32,874	15,664					0,12	1,88	3,406		1,70	26,63	48,251	
	4	17,138	33,008	15,714					0,14	2,20	3,986	3,696	1,96	30,80	55,810	52,031
	5	17,157	33,186	15,872					0,13	2,06	3,739					
	6	17,224	32,863	15,486					0,10	1,55	2,806	3,272				
	7	17,019	32,519	15,348	0,02	0,31	0,556		0,02	0,81	0,566					
	8	17,210	32,778	15,415	0,02	0,31	0,559	0,557	0,02	0,31	0,559	0,557				

51	1	16,998	33,013	15,858					0,09	1,43	2,586		1,26	19,98	36,206	
	2	16,957	32,667	15,556					0,09	1,40	2,537	2,581	1,57	24,42	44,254	40,230
	3	17,200	33,025	15,670					0,07	1,10	1,988		1,62	25,39	45,998	
	4	16,882	32,762	15,724					0,10	1,57	2,849	2,418	1,79	28,15	51,002	48,500
	5	17,035	33,097	15,905					0,13	2,07	3,746					
	6	17,037	32,688	15,498					0,09	1,39	2,527	3,137				
	7	17,032	32,544	15,360	0,02	0,31	0,557		0,02	0,31	0,557					
	8	16,933	32,466	15,381	0,02	0,31	0,557	0,557	0,01	0,15	0,279	0,418				
54	1	17,124	33,127	15,846					0,07	1,11	2,010		1,07	16,96	30,723	
	2	17,131	32,852	15,567					0,08	1,25	2,257	2,133	1,39	21,64	39,208	34,966
	3	17,145	32,950	15,650					0,08	1,25	2,269		1,42	22,22	40,268	
	4	16,555	32,424	15,713					0,09	1,41	2,563	2,416	1,68	26,40	47,834	44,051
	5	17,062	33,093	15,874					0,11	1,75	3,164					
	6	17,071	32,731	15,506					0,09	1,40	2,529	2,846				
	7	17,085	32,586	15,351	0,02	0,31	0,556		0,02	0,31	0,556					
	8	17,135	32,700	15,412	0,02	0,31	0,559	0,557	0,02	0,31	0,559	0,557				
57	1	16,921	32,921	15,843					0,06	0,95	1,722		0,89	14,10	25,550	
	2	17,121	32,799	15,524					0,07	1,09	1,969	1,846	1,20	18,63	33,766	29,653
	3	17,100	32,890	15,635					0,08	1,25	2,266		1,29	20,17	36,547	
	4	17,235	33,100	15,709					0,09	1,41	2,562	2,414	1,58	24,82	44,976	40,761
	5	17,011	33,051	15,883					0,10	1,59	2,878					
	6	17,281	32,916	15,482					0,08	1,24	2,244	2,561				
	7	17,040	32,552	15,360	0,02	0,31	0,557		0,02	0,31	0,557					
	8	16,959	32,493	15,382	0,02	0,31	0,557	0,557	0,01	0,15	0,279	0,418				
60	1	17,058	33,061	15,846					0,06	0,95	1,723		0,78	12,36	22,396	
	2	16,788	32,464	16,522					0,06	0,93	1,688	1,705	1,01	15,68	28,408	25,402
	3	17,092	32,896	15,651					0,07	1,10	1,985		1,12	17,53	31,763	
	4	17,035	32,888	15,688					0,09	1,41	2,560	2,273	1,53	24,02	43,519	37,641
	5	17,144	33,161	15,860					0,09	1,43	2,586					
	6	17,147	32,787	15,487					0,07	1,08	1,964	2,275				
	7	16,978	32,488	15,358	0,02	0,31	0,557		0,02	0,31	0,557					
	8	17,109	32,657	15,396	0,02	0,31	0,558	0,557	0,01	0,15	0,279	0,418				

63	1	17,216	33,211	15,838					0,03	0,48	0,861		0,87	13,78	24,968	
	2	16,955	32,651	15,542					0,03	0,47	0,845	0,853	1,14	17,72	32,105	28,537
	3	17,047	32,856	15,654					0,03	0,47	0,851		1,11	17,38	31,485	
	4	16,515	32,367	15,697					0,05	0,78	1,422	1,137	1,52	23,86	43,232	37,359
	5	17,071	33,073	15,845					0,08	1,27	2,297					
	6	14,708	30,341	15,480					0,06	0,93	1,683	1,990				
	7	17,010	32,519	15,357	0,02	0,31	0,557		0,01	0,15	0,278					
	8	17,150	32,720	15,417	0,02	0,31	0,559	0,558	0,01	0,15	0,279	0,279				
66	1	17,211	33,181	15,813					0,03	0,47	0,860		0,77	12,18	22,064	
	2	17,353	33,060	15,553					0,06	0,93	1,691	1,275	1,62	25,20	45,655	33,859
	3	17,164	32,961	15,642					0,04	0,63	1,134		0,97	15,17	27,493	
	4	16,873	32,692	15,664					0,07	1,10	1,987	1,560	2,35	36,81	66,700	47,097
	5	17,131	33,153	15,865					0,08	1,27	2,300					
	6	17,051	32,650	15,446					0,06	0,93	1,679	1,990				
	7	17,083	32,585	15,350	0,02	0,31	0,556		0,01	0,15	0,278					
	8	17,042	32,588	15,394	0,01	0,15	0,279	0,418	0,01	0,15	0,279	0,279				
69	1	17,029	33,015	15,829					0,04	0,63	1,147		0,66	10,45	18,931	
	2	17,192	32,894	15,548					0,06	0,93	1,690	1,419	1,22	18,97	34,371	26,651
	3	17,010	32,807	15,642					0,04	0,63	1,134		0,82	12,83	23,242	
	4	17,262	33,100	15,683					0,08	1,25	2,273	1,704	2,01	31,52	57,118	40,180
	5	17,146	29,984	12,712					0,07	1,11	2,017					
	6	17,184	32,776	15,441					0,06	0,93	1,679	1,848				
	7	17,162	32,657	15,343	0,02	0,31	0,556		0,01	0,15	0,276					
	8	16,977	32,471	15,342	0,01	0,15	0,278	0,417	0,01	0,15	0,278	0,278				
72	1	16,788	32,776	15,831					0,03	0,47	0,861		0,58	9,18	16,638	
	2	16,986	32,671	15,531					0,06	0,93	1,689	1,275	1,30	20,19	36,585	26,612
	3	17,113	32,910	15,642					0,03	0,47	0,850		0,68	10,64	19,274	
	4	17,203	33,058	15,700					0,05	0,78	1,422	1,136	1,76	27,63	50,068	34,671
	5	17,137	32,175	14,891					0,07	1,11	2,017					
	6	16,830	32,396	15,413					0,06	0,92	1,676	1,846				
	7	17,051	32,574	15,371	0,01	0,15	0,279		0,01	0,15	0,279					
	8	17,224	32,743	15,367	0,01	0,15	0,278	0,278	0,01	0,15	0,278	0,278				

Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF002

Purpose of the study:

To investigate the release rate of SPM 907 from four different formulations of patches. The present experiment is the first in a series of four in which the flux from the four formulations through skin from four different donors is measured. The fluxes through the supportive membrane have been investigated in a previous experiment.

Patch:

Active ingredient: SPM 907
Batch numbers: 20012029, 20012036, 20106043 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Skin donor:

Birth date: 06.12.1983
Sex: female
Skin from: breast
Thickness of dermatomised skin: approximately 290 µm, skin in cell 8 was app. 350 µm.

Diffusion experiment:

Date: 10 to 13 october 2001

Used cells:
diffusion cells with spiral groove (n=8); groove area: 0.552 cm^2;

Separator between acceptor phase and skin/patch:
Silicone sheeting (Silastic sheeting), implant grade elastomer non sterile, non-reinforced;
Manufacturer: Nagor limited, P.O. Box 21, Douglas, Island of Man
Cat. nr. NA 500-1, Thickness 0.125 mm, Lot nr. 11603/1
No special pretreatment, other than cleaning, applied.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr:	Batch
1 & 2	20012029
3 & 4	20012036
5 & 6	20106043
7 & 8	20106061

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 32,0 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

No special observations.

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,008 g/ml

Faktor zur Umrechnung auf cm³= 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	full	volume fraction	8272 µg/ml	µg/fraction	Fraction *F=1.812	Mittelwert	DiOH µg/ml	µg/fraction	FractionxF µg/cm²	Mittelwert	Diacetat µg/ml	µg/fraction	FractionxF µg/cm²	Mittelwert
3	1	17,063	33,268	16,075					0,02	0,322	0,583		0	0	0,000	
	2	17,231	33,311	15,951					0,02	0,319	0,578	0,580	0	0	0,000	0,000
	3	17,137	33,225	15,959					0,01	0,160	0,289		0	0	0,000	
	4	17,069	33,212	16,014					0,01	0,160	0,290	0,290	0	0	0,000	0,000
	5	17,158	33,501	16,212					0,01	0,162	0,294					
	6	17,154	32,990	15,709					0,01	0,157	0,285	0,289				
	7	17,265	32,997	15,606	0	0,000			0,01	0,156	0,283					
	8	17,037	32,889	15,725	0	0,000			0,01	0,157	0,285	0,284				
6	1	16,973	33,218	16,115					0,00	0	0,000		0	0,000	0,000	
	2	16,968	33,123	16,026					0,00	0	0,000		0	0,000	0,000	0,000
	3	16,925	33,047	15,993					0,00	0	0,000		0	0,000	0,000	
	4	17,253	33,391	16,009					0,00	0	0,000		0,01	0,160	0,290	0,145
	5	17,140	33,511	16,240					0,00	0	0,000					
	6	17,272	33,188	15,789					0,00	0	0,000					
	7	17,198	32,921	15,597	0	0,000			0,00	0	0,000					
	8	17,144	33,052	15,781	0	0,000			0,00	0	0,000					
9	1	17,039	33,261	16,092					0,00	0	0,000		0	0,000	0,000	
	2	17,064	33,200	16,007					0,00	0	0,000		0,01	0,160	0,290	0,145
	3	17,219	33,343	15,995					0,00	0	0,000		0,05	0,800	1,449	
	4	17,036	33,172	16,007					0,00	0	0,000		0,01	0,160	0,290	0,870
	5	17,174	33,553	16,248					0,00	0	0,000					
	6	17,078	32,965	15,760					0,00	0	0,000					
	7	17,062	32,796	15,606	0	0,000			0,00	0	0,000					
	8	17,156	33,061	15,778	0	0,000			0,00	0	0,000					
12	1	17,272	33,469	16,067					0,00	0	0,000			0,000	0,000	
	2	17,232	33,364	16,003					0,00	0	0,000		0,01	0,160	0,290	0,145
	3	17,232	33,359	15,998					0,00	0	0,000		0,06	0,960	1,739	
	4	17,047	33,169	15,993					0,00	0	0,000		0,01	0,160	0,290	1,015
	5	17,264	33,626	16,231					0,00	0	0,000					
	6	17,188	33,089	15,774					0,00	0	0,000					
	7	17,069	32,813	15,618	0	0,000			0,00	0	0,000					
	8	17,162	33,066	15,777	0	0,000			0,00	0	0,000					

15	1	17,133	33,356	16,093					0,01	0,161	0,292			0,000	0,000			
	2	17,221	33,339	15,989					0,01	0,160	0,290	0,291	0,03	0,480	0,869	0,435		
	3	17,159	33,254	15,966					0,01	0,160	0,289		0,08	1,277	2,314			
	4	17,080	33,187	15,978					0,00	0,000	0,000	0,145	0,01	0,160	0,290	1,302		
	5	17,144	33,513	16,238					0,01	0,162	0,294							
	6	16,950	32,833	15,756					0,01	0,158	0,285	0,290						
	7	17,113	32,849	15,610	0	0,000			0,01	0,156	0,283							
	8	16,931	32,855	15,797	0	0,000			0,00	0,000	0,000	0,141						
18	1	17,087	33,288	16,071					0,01	0,161	0,291		0	0,000	0,000			
	2	16,704	32,823	15,990					0,01	0,160	0,290	0,290	0,03	0,480	0,869	0,435		
	3	16,880	33,009	16,000					0,00	0,000	0,000		0,08	1,280	2,319			
	4	17,119	33,251	16,003					0,00	0,000	0,000	0,000	0,01	0,160	0,290	1,305		
	5	16,977	33,332	16,224					0,00	0,000	0,000							
	6	17,091	32,968	15,750					0,01	0,157	0,285	0,143						
	7	16,910	32,651	15,615	0	0,000			0,01	0,156	0,283							
	8	16,902	32,819	15,790	0	0,000			0,02	0,316	0,572	0,428						
21	1	16,564	32,677	15,994					0,00	0,000	0,000		0	0,000	0,000			
	2	17,028	33,082	15,925					0,00	0,000	0,000	0,000	0,04	0,637	1,154	0,577		
	3	17,191	33,238	15,919					0,00	0,000	0,000		0,07	1,114	2,019			
	4	17,182	33,231	15,921					0,00	0,000	0,000	0,000	0,02	0,318	0,577	1,298		
	5	17,090	33,395	16,174					0,01	0,162	0,293							
	6	17,098	32,920	15,695					0,00	0,000	0,000	0,147						
	7	17,147	32,805	15,533	0	0,000			0,01	0,155	0,281							
	8	17,063	32,897	15,707	0	0,000			0,00	0,000	0,000	0,141						
24	1	16,779	32,906	15,998					0,00	0,000	0,000		0,01	0,160	0,290			
	2	17,282	33,307	15,897					0,01	0,159	0,288	0,144	0,05	0,795	1,440	0,865		
	3	17,038	33,072	15,906					0,01	0,159	0,288		0,10	1,591	2,882			
	4	17,057	33,100	15,915					0,01	0,159	0,288	0,288	0,04	0,637	1,153	2,018		
	5	16,955	33,249	16,164					0,01	0,162	0,293							
	6	17,161	32,951	15,664					0,00	0,000	0,000	0,146						
	7	17,089	32,759	15,545	0	0,000			0,01	0,155	0,282							
	8	17,303	33,151	15,721	0	0,000			0,01	0,157	0,285	0,283						

27	1	17,156	33,272	15,987					0,01	0,160	0,290		0,01	0,160	0,290			
	2	17,177	33,213	15,908					0,00	0,000	0,000	0,145	0,05	0,795	1,441	0,865		
	3	17,322	33,345	15,895					0,01	0,159	0,288		0,09	1,431	2,592			
	4	17,155	33,189	15,906					0,01	0,159	0,288	0,288	0,05	0,795	1,441	2,017		
	5	16,824	33,108	16,154					0,00	0,000	0,000							
	6	17,098	32,893	15,669					0,00	0,000	0,000	0,000						
	7	17,086	32,719	15,508	0	0,000			0,01	0,155	0,281							
	8	17,046	32,877	15,704	0	0,000			0,00	0,000	0,000	0,141						
30	1	17,227	33,305	15,949					0,01	0,159	0,289		0,02	0,319	0,578			
	2	17,126	33,126	15,872					0,00	0,000	0,000	0,145	0,06	0,952	1,726	1,152		
	3	17,123	33,142	15,891					0,00	0,000	0,000		0,07	1,112	2,016			
	4	17,102	33,119	15,889					0,01	0,159	0,288	0,144	0,06	0,953	1,727	1,872		
	5	17,133	33,400	16,137					0,01	0,161	0,292							
	6	17,200	32,962	15,636					0,01	0,156	0,283	0,288						
	7	17,103	32,765	15,537	0	0,000			0,01	0,155	0,282							
	8	17,006	32,812	15,677	0	0,000			0,01	0,157	0,284	0,283						
33	1	17,009	33,103	15,965					0,01	0,160	0,289		0,03	0,479	0,868			
	2	17,187	33,175	15,860					0,01	0,159	0,287	0,288	0,06	0,952	1,724	1,296		
	3	17,167	33,152	15,857					0,01	0,159	0,287		0,08	1,269	2,299			
	4	17,058	33,041	15,855					0,02	0,317	0,575	0,431	0,09	1,427	2,586	2,442		
	5	16,977	33,221	16,114					0,01	0,161	0,292							
	6	17,230	32,996	15,640					0,01	0,156	0,283	0,288						
	7	17,107	32,737	15,505	0	0,000			0,01	0,155	0,281							
	8	17,179	32,994	15,688	0	0,000			0,00	0,000	0,000	0,140						
36	1	17,411	33,461	15,922					0,01	0,159	0,288		0,03	0,478	0,865			
	2	17,053	33,025	15,844					0,01	0,158	0,287	0,288	0,06	0,951	1,723	1,294		
	3	16,895	32,897	15,874					0,03	0,476	0,863		0,08	1,270	2,301			
	4	17,271	33,262	15,863					0,01	0,159	0,287	0,575	0,10	1,586	2,874	2,588		
	5	17,231	33,482	16,121					0,01	0,161	0,292							
	6	17,189	32,931	15,616					0,01	0,156	0,283	0,288						
	7	17,143	32,777	15,509	0	0,000			0,01	0,155	0,281							
	8	16,937	32,718	15,655	0	0,000			0,01	0,157	0,284	0,282						

39	1	16,980	32,874	15,767					0,02	0,315	0,571		0,04	0,631	1,143		
	2	16,918	32,706	15,662					0,02	0,313	0,568	0,569	0,07	1,096	1,987	1,565	
	3	16,981	32,769	15,662					0,02	0,313	0,568		0,08	1,253	2,270		
	4	16,992	32,801	15,682					0,03	0,470	0,852	0,710	0,1	1,568	2,842	2,556	
	5	16,962	33,025	15,934					0,01	0,159	0,289						
	6	17,245	32,812	15,442					0,01	0,154	0,280	0,284					
	7	17,178	32,609	15,307	0	0,000			0,01	0,153	0,277						
	8	17,178	32,765	15,462	0	0,000			0,01	0,155	0,280	0,279					
42	1	17,126	33,013	15,760					0,01	0,158	0,286		0,04	0,630	1,142		
	2	16,919	32,716	15,671					0,10	1,567	2,840	1,563	0,07	1,097	1,988	1,565	
	3	17,302	33,113	15,684					0,02	0,314	0,568		0,10	1,568	2,842		
	4	17,237	33,036	15,673					0,04	0,627	1,136	0,852	0,15	2,351	4,260	3,551	
	5	17,248	33,294	15,918					0,01	0,159	0,288						
	6	14,706	30,240	15,410					0,01	0,154	0,279	0,284					
	7	17,169	32,612	15,319	0	0,000			0,01	0,153	0,278						
	8	17,208	32,824	15,491	0	0,000			0,01	0,155	0,281	0,279					
45	1	16,976	32,857	15,754					0,02	0,315	0,571		0,05	0,788	1,427		
	2	16,941	32,733	15,666					0,01	0,157	0,284	0,427	0,08	1,253	2,271	1,849	
	3	17,075	32,886	15,684					0,02	0,314	0,568		0,12	1,882	3,410		
	4	16,946	32,755	15,682					0,03	0,470	0,852	0,710	0,16	2,509	4,547	3,979	
	5	17,065	33,125	15,931					0,01	0,159	0,289						
	6	17,252	32,829	15,452					0,01	0,155	0,280	0,284					
	7	16,465	31,911	15,322	0	0,000			0,01	0,153	0,278						
	8	17,074	32,688	15,489	0	0,000			0,01	0,155	0,281	0,279					
48	1	17,011	32,888	15,750					0	0,000	0,000		0,05	0,787	1,427		
	2	17,364	33,150	15,660					0,01	0,157	0,284	0,142	0,08	1,253	2,270	1,848	
	3	17,181	32,987	15,679					0,01	0,157	0,284		0,10	1,568	2,841		
	4	17,084	32,889	15,678					0,03	0,470	0,852	0,568	0,17	2,665	4,830	3,835	
	5	17,023	33,075	15,923					0,01	0,159	0,289						
	6	17,106	32,647	15,417					0,01	0,154	0,279	0,284					
	7	17,072	32,525	15,329	0	0,000			0,01	0,153	0,278						
	8	17,186	32,806	15,495	0	0,000			0,01	0,155	0,281	0,279					

51	1	17,008	32,899	15,764					0,02	0,315	0,571		0,08	1,261	2,285		
	2	17,008	32,784	15,650					0,02	0,313	0,567	0,569	0,11	1,721	3,119	2,702	
	3	17,053	32,858	15,678					0,02	0,314	0,568		0,17	2,665	4,830		
	4	17,052	32,846	15,668					0,04	0,627	1,136	0,852	0,23	3,604	6,530	5,680	
	5	17,074	33,113	15,911					0,01	0,159	0,288						
	6	17,090	32,645	15,430					0,01	0,154	0,280	0,284					
	7	16,921	32,368	15,323	0	0,000			0,01	0,153	0,278						
	8	17,188	32,801	15,488	0	0,000			0,01	0,155	0,281	0,279					
54	1	17,024	32,887	15,736					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,143	32,909	15,640					0,01	0,156	0,283	0,427	0,10	1,564	2,834	2,558	
	3	17,206	32,999	15,667					0,02	0,313	0,568		0,17	2,663	4,826		
	4	17,112	32,902	15,664					0,05	0,783	1,419	0,993	0,25	3,916	7,096	5,961	
	5	17,024	33,057	15,905					0,01	0,159	0,288						
	6	17,029	32,589	15,435					0,01	0,154	0,280	0,284					
	7	16,997	32,427	15,306	0	0,000			0,01	0,153	0,277						
	8	16,884	32,487	15,478	0	0,000			0,01	0,155	0,280	0,279					
57	1	17,215	33,077	15,735					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,179	32,949	15,644					0,02	0,313	0,567	0,569	0,10	1,564	2,835	2,558	
	3	17,150	32,917	15,641					0,03	0,469	0,850		0,16	2,503	4,535		
	4	17,161	32,944	15,667					0,05	0,783	1,418	1,134	0,26	4,071	7,376	5,955	
	5	17,340	33,386	15,918					0,01	0,159	0,288						
	6	17,121	32,634	15,389					0,01	0,154	0,279	0,284					
	7	17,160	32,589	15,305	0	0,000			0,01	0,153	0,277						
	8	17,061	32,656	15,470	0	0,000			0,01	0,155	0,280	0,279					
60	1	17,166	33,031	15,738					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,098	32,868	15,644					0,02	0,313	0,567	0,569	0,16	2,503	4,535	3,408	
	3	16,869	32,654	15,659					0,03	0,470	0,851		0,18	2,819	5,107		
	4	17,014	32,800	15,660					0,05	0,783	1,419	1,135	0,26	4,072	7,378	6,242	
	5	17,138	33,174	15,908					0,01	0,159	0,288						
	6	17,178	32,701	15,399					0,01	0,154	0,279	0,284					
	7	16,970	32,401	15,307	0	0,000			0,01	0,153	0,277						
	8	17,166	32,725	15,434	0	0,000			0,01	0,154	0,280	0,279					

63	1	17,194	33,066	15,745					0,02	0,315	0,571		0,08	1,260	2,282		
	2	16,957	32,724	15,641					0,02	0,313	0,567	0,569	0,16	2,503	4,535	3,408	
	3	17,042	32,829	15,661					0,03	0,470	0,851		0,19	2,976	5,392		
	4	17,123	32,896	15,647					0,05	0,782	1,418	1,134	0,26	4,068	7,371	6,382	
	5	17,156	33,179	15,895					0,01	0,159	0,288						
	6	17,022	32,563	15,417					0,01	0,154	0,279	0,284					
	7	17,128	32,542	15,291	0	0,000			0,02	0,306	0,554						
	8	17,162	32,764	15,477	0	0,000			0,01	0,155	0,280	0,417					
66	1	16,513	32,343	15,703					0,02	0,314	0,569		0,08	1,256	2,276		
	2	16,996	32,752	15,630					0,02	0,313	0,566	0,568	0,15	2,344	4,248	3,262	
	3	17,050	32,829	15,653					0,03	0,470	0,851		0,19	2,974	5,389		
	4	16,604	32,400	15,670					0,04	0,627	1,136	0,993	0,26	4,074	7,382	6,386	
	5	17,202	33,230	15,900					0,01	0,159	0,288						
	6	17,275	32,800	15,401					0,01	0,154	0,279	0,284					
	7	17,185	32,630	15,321	0	0,000			0,01	0,153	0,278						
	8	17,186	32,776	15,465	0	0,000			0,01	0,155	0,280	0,279					
69	1	17,063	32,920	15,730					0,02	0,315	0,570		0,08	1,258	2,280		
	2	17,180	32,936	15,630					0,02	0,313	0,566	0,568	0,15	2,344	4,248	3,264	
	3	17,137	32,926	15,663					0,02	0,313	0,568		0,19	2,976	5,392		
	4	17,093	32,871	15,652					0,04	0,626	1,134	0,851	0,24	3,756	6,807	6,099	
	5	17,149	33,192	15,915					0,01	0,159	0,288						
	6	17,113	32,616	15,379					0,01	0,154	0,279	0,284					
	7	17,148	32,569	15,298	0	0,000			0,01	0,153	0,277						
	8	17,045	32,631	15,461	0	0,000			0,01	0,155	0,280	0,279					
72	1	17,201	33,058	15,730					0,02	0,315	0,570		0,08	1,258	2,280		
	2	17,072	32,832	15,634					0,02	0,313	0,567	0,568	0,14	2,189	3,966	3,123	
	3	17,053	32,826	15,647					0,02	0,313	0,567		0,20	3,129	5,670		
	4	17,204	32,981	15,651					0,04	0,626	1,134	0,851	0,26	4,069	7,373	6,522	
	5	16,992	33,009	15,889					0,01	0,159	0,288						
	6	17,046	32,564	15,394					0,01	0,154	0,279	0,283					
	7	17,144	32,549	15,282	0	0,000			0,01	0,153	0,277						
	8	17,032	32,628	15,471	0	0,000			0,01	0,155	0,280	0,279					

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20003028
Soilgehalt :	4,0 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN168A-B	Analysendatum :	28.03.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 9 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=170 µm; 2=175 µm; 3=148 µm, 33,3g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C
;

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	MW	SD	MW
3	1,15	0,81	2,25	1,40	0,76	0,31
6	2,15	1,95	3,76	2,62	0,99	0,54
24	4,13	4,78	5,19	4,70	0,54	0,99
30	4,30	5,19	5,23	4,91	0,53	1,02
48	4,42	5,40	5,25	5,02	0,53	1,03

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 6,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	1,98	mg
Regressionskoeffizient (m) =	0,06	mg/h
Korrelationskoeffizient (r) =	0,88839	

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,26	0,20	0,32	0,26	0,06
6	0,47	0,39	0,62	0,48	0,07
24	1,07	1,05	0,93	1,02	0,07
30	1,13	1,10	0,98	1,06	0,09
48	1,19	1,15	0,98	1,10	0,11

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,35	mg
Regressionskoeffizient (m) =	0,02	mg/h
Korrelationskoeffizient (r) =	0,90552	

$Q = t$ $Q = t \cdot m + b$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20004038
Soligehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IN189 A,B	Analysendatum :	17.04.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 7 Wochen lebend, 2 Wochen TK-Schrank; SKH-1♂
1=159 µm; 2=165 µm; 3=146 µm, 31,9 g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	MW	SD	MW
3	0,14	0,15	0,20	0,16	0,03	0,04
6	1,21	1,17	1,28	1,22	0,06	0,22
24	2,27	2,17	2,35	2,27	0,09	0,41
30	2,48	2,37	2,54	2,46	0,09	0,43
48	2,75	2,63	2,75	2,71	0,07	0,46

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 6,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,62	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,89901	

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,07	0,07	0,08	0,07	0,01
6	0,38	0,39	0,37	0,38	0,01
24	0,71	0,72	0,68	0,71	0,02
30	0,77	0,77	0,72	0,75	0,03
48	0,83	0,83	0,77	0,81	0,03

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,21	mg
Regressionskoeffizient (m) =	0,02	mg/h
Korrelationskoeffizient (r) =	0,89243	

$Q = t$ $Q = t \cdot m + b$
Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20004039
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IN189 A,B	Analysendatum :	17.04.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 7 Wochen lebend, 2 Wochen TK-Schrank; SKH-1♂
1=180 µm; 2=165 µm; 3=143 µm, 34,0 g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	MW	SD	MW
3	0,11	0,25	0,59	0,32	0,25	0,09
6	0,80	1,04	1,17	1,03	0,13	0,22
24	1,71	1,82	1,74	1,76	0,05	0,37
30	1,84	1,92	1,78	1,85	0,07	0,38
48	1,97	1,99	1,81	1,92	0,10	0,39

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 8,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,65	mg
Regressionskoeffizient (m) =	0,03	mg/h
Korrelationskoeffizient (r) =	0,87148	

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,06	0,08	0,13	0,09	0,04
6	0,32	0,33	0,34	0,33	0,01
24	0,60	0,58	0,55	0,58	0,02
30	0,64	0,60	0,57	0,60	0,03
48	0,68	0,63	0,58	0,63	0,05

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,20	mg
Regressionskoeffizient (m) =	0,01	mg/h
Korrelationskoeffizient (r) =	0,87353	

$Q \approx t$ $Q = t \cdot m + b$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF003

Purpose of the study:
To investigate the release rate of SPM 907 from four different formulations of patches. The present experiment is the second in a series of four in which the flux from the four formulations through skin from four different donors is measured. Because of low flux values in the first experiment in this series, the silastic sheeting supportive membrane has been replaced with dialysis membrane.

Patch:
Active ingredient: SPM 907
Batch numbers: 20012029, 20012036 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Skin donor:
Birth date: 1969
Sex: female
Skin from: abdomen (belly)
Thickness of dermatomised skin: approximately 240 µm

Diffusion experiment:

Date: 15 to 18 november 2001

Used cells:
diffusion cells with spiral groove (n=6); groove area: 0.552 cm^2.

Separator between acceptor phase and skin/patch:
Diachema dialysis membrane, type 10.14, supplied by Dianorm, München, Germany.
Manufactured from neutral cellulose, molar weight cut-off: 5000, thickness (dry): 25 µm.
Pretreated according to the manufacturer's recommendations.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr:	Batch
1 & 2	20106061
3 & 4	20012029
5 & 6	20012036

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 31,9 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.
1.) The total area of good quality skin on the delivered pieces allowed the punch-out of no more than six disks for use in the experiment. Therefore, only three of the four batches were tested.
2.) The skin disk in cell 1 contained a thinner area on one side.
3.) The skin disk in cell 6 was thinner on the whole area.
4.) The skin disks in cells 2, 3, 4 and 6 showed spots from the blue marker used to mark unusable areas on the skin pieces. Traces of the blue dye might be found in the corresponding diffusion samples.

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,007 g/ml | Faktor zur Umrechnung auf cm³= 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes (g) full	volume fractions (ml)	8272 µg/ml	8272 µg/fraction	Fraction *F=1.812	Mittelwert	DIOH µg/ml	DIOH µg/fraction	FractionxF µg/cm²	Mittelwert	Diacetat µg/ml	Diacetat µg/fraction	FractionxF µg/cm²	Mittelwert	
3	1	16,976	33,097	16,005	0,01	0,160	0,290005		0,03	0,480	0,870						
	2	17,155	32,862	15,594	0	0,000	0,000	0,145	0,02	0,312	0,565	0,718					
	3	16,962	32,718	15,642					0,04	0,626	1,134		0,56	8,760	15,873		3
	4	16,966	32,573	15,494					0,02	0,310	0,562	0,848	0,02	0,310	0,562	8,217	
	5	17,028	32,635	15,494					0,02	0,310	0,562		0,02	0,310	0,562		
	6	16,968	32,350	15,271					0,06	0,916	1,660	1,111	0,38	5,803	10,515	5,538	
6	1	17,156	33,289	16,017	0,01	0,160	0,290		0,04	0,641	1,161						
	2	17,179	32,907	15,615	0	0,000	0,000	0,145	0,02	0,312	0,566	0,863					
	3	17,281	33,008	15,614					0,09	1,405	2,546		0,61	9,524	17,258		6
	4	17,157	32,757	15,487					0,02	0,310	0,561	1,554	0,01	0,155	0,281	8,769	
	5	17,113	32,717	15,491					0,09	1,394	2,526		0,05	0,775	1,404		
	6	17,171	32,548	15,266					0,09	1,374	2,490	2,508	0,39	5,954	10,788	6,096	
9	1	16,873	33,002	16,013	0,01	0,160	0,290		0,06	0,961	1,741						
	2	17,271	32,986	15,604	0	0,000	0,000	0,145	0,03	0,468	0,848	1,295					
	3	17,027	32,743	15,603					0,1	1,560	2,827		0,57	8,893	16,115		9
	4	17,229	32,838	15,496					0,06	0,930	1,685	2,256	0,02	0,310	0,562	8,338	
	5	16,820	32,426	15,493					0,14	2,169	3,930		0,09	1,394	2,527		
	6	17,023	32,434	15,300					0,12	1,836	3,327	3,629	0,40	6,120	11,089	6,808	
12	1	17,111	33,253	16,026	0,02	0,321	0,581		0,07	1,122	2,033						
	2	17,046	32,781	15,621	0,01	0,156	0,283	0,432	0,04	0,625	1,132	1,582					
	3	17,145	32,896	15,637					0,12	1,876	3,400		0,57	8,913	16,151		12
	4	16,727	32,342	15,502					0,09	1,395	2,528	2,964	0,05	0,775	1,405	8,778	
	5	17,276	32,908	15,519					0,19	2,949	5,343		0,13	2,017	3,656		
	6	16,950	32,391	15,330					0,13	1,993	3,611	4,477	0,41	6,285	11,389	7,522	
15	1	17,230	33,365	16,019	0,03	0,481	0,871		0,08	1,281	2,322						
	2	17,138	32,670	15,619	0,01	0,156	0,283	0,577	0,05	0,781	1,415	1,869					
	3	17,042	32,780	15,624					0,16	2,500	4,530		0,55	8,593	15,571		15
	4	17,072	32,700	15,515					0,11	1,707	3,093	3,811	0,10	1,552	2,811	9,191	
	5	16,945	32,590	15,532					0,2	3,106	5,629		0,17	2,640	4,785		
	6	17,206	32,608	15,291					0,12	1,835	3,325	4,477	0,45	6,881	12,468	8,626	
18	1	17,209	33,094	15,770	0,04	0,631	1,143		0,09	1,419	2,572						
	2	17,045	32,564	15,407	0,02	0,308	0,558	0,851	0,06	0,924	1,675	2,123					
	3	16,990	32,502	15,400					0,19	2,926	5,302		0,53	8,162	14,790		18
	4	17,183	32,564	15,270					0,14	2,138	3,874	4,588	0,13	1,985	3,597	9,193	
	5	17,156	32,562	15,295					0,24	3,671	6,651		0,22	3,365	6,097		
	6	17,167	32,369	15,092					0,18	2,717	4,923	5,787	0,46	6,942	12,580	9,338	

21	1	16,907	32,790	15,768	0,04	0,631	1,143		0,10	1,577	2,857						21
	2	16,968	32,448	15,368	0,02	0,307	0,557	0,850	0,07	1,076	1,949	2,403					
	3	17,117	32,616	15,387					0,21	3,231	5,855		0,55	8,463	15,335		
	4	17,042	32,410	15,257					0,18	2,746	4,976	5,416	0,17	2,594	4,700	10,017	
	5	17,054	32,458	15,293					0,22	3,364	6,096		0,41	6,270	11,361		
	6	17,198	32,398	15,090					0,20	3,018	5,469	5,783	0,48	7,243	13,125	12,243	
24	1	16,873	32,728	15,741	0,05	0,787	1,426		0,10	1,574	2,852				0,000		24
	2	17,067	32,545	15,366	0,02	0,307	0,557	0,991	0,07	1,076	1,949	2,401					
	3	16,083	31,559	15,364					0,22	3,380	6,125		0,57	8,758	15,869		
	4	16,896	32,284	15,277					0,18	2,750	4,983	5,554	0,21	3,208	5,813	10,841	
	5	17,212	32,631	15,308					0,28	4,286	7,767		0,34	5,205	9,431		
	6	17,140	32,326	15,076					0,20	3,015	5,464	6,615	0,59	8,895	16,118	12,774	
27	1	17,160	33,073	15,778	0,05	0,789	1,430		0,10	1,578	2,859						27
	2	17,053	32,549	15,364	0,03	0,462	0,836		0,08	1,231	2,230	2,545					
	3	17,164	32,652	15,376					0,23	3,537	6,408		0,58	8,918	16,160		
	4	16,663	32,038	15,264					0,23	3,511	6,361	6,385	0,25	3,816	6,915	11,537	
	5	17,017	32,418	15,290					0,30	4,587	8,312		0,39	5,963	10,805		
	6	16,972	32,159	15,077					0,23	3,466	6,284	7,298	0,60	9,046	16,392	13,599	
30	1	17,067	32,918	15,737	0,04	0,629	1,141		0,09	1,416	2,566						30
	2	16,897	32,361	15,352	0,03	0,461	0,835	0,988	0,08	1,228	2,225	2,396					
	3	17,223	32,729	15,394					0,23	3,541	6,416		0,6	9,236	16,737		
	4	16,837	32,201	15,253					0,21	3,203	5,804	6,110	0,26	4,271	7,799	12,238	
	5	17,058	32,469	15,300					0,31	4,743	8,594		0,45	6,885	12,475		
	6	17,166	32,341	15,066					0,25	3,766	6,825	7,709	0,65	9,793	17,744	15,110	
33	1	17,083	32,950	15,753	0,04	0,630	1,142		0,09	1,418	2,569						33
	2	17,175	32,658	15,371	0,03	0,461	0,836	0,969	0,08	1,230	2,228	2,399					
	3	17,093	32,576	15,371					0,23	3,535	6,406		0,61	9,376	16,990		
	4	17,162	32,542	15,269					0,22	3,359	6,087	6,246	0,31	4,739	8,577	12,784	
	5	17,200	32,604	15,293					0,32	4,894	8,867		0,51	7,799	14,132		
	6	17,176	32,348	15,063					0,25	3,766	6,823	7,845	0,69	10,393	18,832	16,482	
36	1	16,973	32,840	15,753	0,04	0,630	1,142		0,09	1,418	2,569						36
	2	17,148	32,615	15,355	0,02	0,307	0,556	0,849	0,08	1,228	2,226	2,397					
	3	17,007	32,522	15,403					0,24	3,697	6,698		0,64	9,858	17,863		
	4	17,130	32,488	15,247					0,22	3,354	6,078	6,388	0,35	5,337	9,670	13,766	
	5	17,090	32,497	15,296					0,33	5,048	9,146		0,57	8,719	15,798		
	6	16,932	32,123	15,081					0,27	4,072	7,378	8,262	0,73	11,009	19,949	17,874	

39	1	17,146	32,975	15,715	0,03	0,471	0,854		0,08	1,257	2,278						39
	2	17,008	32,444	15,325	0,02	0,306	0,555	0,705	0,07	1,073	1,944	2,111					
	3	16,948	32,409	15,349					0,21	3,223	5,841		0,72	11,052	20,026		
	4	17,214	32,555	15,230					0,21	3,196	5,795	5,818	0,40	6,092	11,039	15,532	
	5	17,014	32,398	15,273					0,31	4,735	8,579		0,68	10,386	18,819		
	6	16,908	32,071	15,054					0,24	3,613	6,547	7,563	0,84	12,645	22,913	20,866	
42	1	16,962	32,797	15,721	0,03	0,472	0,855		0,08	1,258	2,279						42
	2	17,083	32,531	15,337	0,02	0,307	0,556	0,705	0,07	1,074	1,945	2,112					
	3	17,216	32,668	15,341					0,20	3,068	5,559		0,71	10,892	19,736		
	4	17,242	32,590	15,297					0,21	3,200	5,798	5,679	0,45	6,857	12,424	16,080	
	5	17,069	32,455	15,275					0,31	4,735	8,580		0,73	11,151	20,205		
	6	17,143	32,295	15,043					0,23	3,460	6,269	7,425	0,87	13,087	23,714	21,960	
45	1	17,027	32,843	15,702	0,03	0,471	0,854		0,07	1,099	1,992						45
	2	17,210	32,654	15,333	0,02	0,307	0,556	0,705	0,07	1,073	1,946	1,968					
	3	17,012	32,480	15,356					0,20	3,071	5,565		0,73	11,210	20,313		
	4	17,020	32,371	15,240					0,21	3,200	5,799	5,682	0,46	7,011	12,703	16,508	
	5	16,552	31,943	15,280					0,30	4,584	8,306		0,78	11,918	21,596		
	6	17,046	32,200	15,046					0,23	3,461	6,270	7,288	0,89	13,391	24,264	22,930	
48	1	17,134	32,969	15,721	0,02	0,314	0,570		0,07	1,100	1,994						48
	2	17,055	32,473	15,307	0,02	0,306	0,555	0,562	0,07	1,071	1,942	1,968					
	3	16,958	32,418	15,348					0,20	3,070	5,562		0,73	11,204	20,302		
	4	17,249	32,593	15,233					0,20	3,047	5,521	5,541	0,48	7,312	13,249	16,776	
	5	17,143	32,504	15,250					0,32	4,880	8,843		0,81	12,353	22,383		
	6	17,088	32,249	15,052					0,23	3,462	6,273	7,558	0,92	13,847	25,092	23,737	
51	1	16,902	32,717	15,701	0,02	0,314	0,569		0,06	0,942	1,707						51
	2	17,055	32,484	15,318	0,02	0,306	0,555	0,562	0,06	0,919	1,665	1,686					
	3	17,161	32,602	15,330					0,18	2,759	5,000		0,75	11,497	20,833		
	4	16,964	32,291	15,216					0,20	3,043	5,514	5,257	0,50	7,608	13,786	17,310	
	5	17,254	32,640	15,275					0,30	4,583	8,303		0,84	12,831	23,250		
	6	17,027	32,175	15,039					0,22	3,309	5,995	7,149	0,92	13,836	25,070	24,160	
54	1	16,655	32,456	15,687	0,02	0,314	0,568		0,06	0,941	1,705						54
	2	17,138	32,557	15,308	0,02	0,306	0,555	0,562	0,06	0,918	1,664	1,685					
	3	17,147	32,600	15,342					0,18	2,761	5,004		0,76	11,660	21,127		
	4	17,200	32,534	15,223					0,20	3,045	5,517	5,260	0,53	8,068	14,620	17,874	
	5	17,145	32,516	15,260					0,29	4,425	8,019		0,87	13,276	24,057		
	6	17,041	32,180	15,030					0,23	3,457	6,264	7,141	0,94	14,128	25,600	24,828	

57	1	16,473	32,284	15,697	0,02	0,314	0,569		0,06	0,942	1,707						57
	2	17,210	32,641	15,320	0,01	0,153	0,278	0,423	0,06	0,919	1,666	1,686					
	3	17,323	32,765	15,331					0,18	2,760	5,000		0,77	11,805	21,390		
	4	17,163	32,488	15,215					0,19	2,891	5,236	5,119	0,55	8,368	15,164	18,277	
	5	17,165	32,549	15,273					0,28	4,276	7,749		0,90	13,746	24,907		
	6	16,977	32,131	15,045					0,22	3,310	5,997	6,873	0,95	14,292	25,898	25,403	
60	1	16,585	32,393	15,694	0,01	0,157	0,284		0,06	0,942	1,706						60
	2	17,265	32,683	15,307	0,01	0,153	0,277	0,281	0,06	0,918	1,664	1,685					
	3	16,940	32,380	15,329					0,18	2,759	5,000		0,77	11,803	21,387		
	4	17,035	32,375	15,229					0,19	2,894	5,243	5,121	0,58	8,833	16,005	18,696	
	5	17,061	32,433	15,261					0,27	4,120	7,466		0,92	14,040	25,441		
	6	17,231	32,396	15,056					0,21	3,162	5,729	6,598	0,98	14,754	26,735	26,088	
63	1	17,127	32,942	15,701	0,01	0,157	0,285		0,05	0,785	1,423						63
	2	17,210	32,633	15,312	0,01	0,153	0,277	0,281	0,06	0,919	1,665	1,544					
	3	17,175	32,621	15,335					0,17	2,607	4,724		0,81	12,421	22,507		
	4	17,224	32,553	15,218					0,18	2,739	4,964	4,844	0,59	8,979	16,270	19,388	
	5	16,702	32,105	15,292					0,28	4,282	7,758		0,94	14,374	26,046		
	6	17,089	32,242	15,044					0,21	3,159	5,724	6,741	0,95	14,291	25,896	25,971	
66	1	16,633	32,643	15,696	0,01	0,157	0,284		0,05	0,785	1,422						66
	2	17,160	32,577	15,306	0,01	0,153	0,277	0,281	0,05	0,765	1,387	1,404					
	3	17,115	32,588	15,361					0,16	2,458	4,454		0,79	12,135	21,989		
	4	17,140	32,485	15,234					0,19	2,895	5,245	4,849	0,60	9,141	16,563	19,276	
	5	17,197	32,573	15,265					0,28	4,274	7,745		1,00	15,265	27,660		
	6	17,144	32,307	15,054					0,21	3,161	5,728	6,737	0,97	14,602	26,459	27,060	
69	1	17,173	32,988	15,701	0,01	0,157	0,285		0,05	0,785	1,423						69
	2	17,090	32,510	16,309	0,01	0,153	0,277	0,281	0,05	0,765	1,387	1,405					
	3	17,132	32,564	15,321					0,16	2,451	4,442		0,81	12,410	22,486		
	4	17,172	32,494	15,211					0,22	3,347	6,064	5,253	0,76	11,561	20,948	21,717	
	5	17,065	32,442	15,266					0,23	3,511	6,362		0,84	12,823	23,236		
	6	17,072	32,215	15,034					0,2	3,007	5,448	5,905	0,97	14,583	26,424	24,830	
72	1	17,117	32,921	15,690	0,01	0,157	0,284		0,05	0,784	1,422						72
	2	17,121	32,593	15,301	0,01	0,153	0,277	0,281	0,05	0,765	1,386	1,404					
	3	17,119	32,585	15,354					0,17	2,610	4,730		0,82	12,591	22,814		
	4	17,141	32,497	15,245					0,18	2,744	4,972	4,851	0,65	9,909	17,956	20,385	
	5	17,205	32,612	15,296					0,25	3,824	6,929		0,99	15,143	27,439		
	6	17,073	32,246	15,064					0,19	2,862	5,186	6,058	0,99	14,913	27,022	27,231	

EXHIBIT F

US006713464B1

(12) **United States Patent**
Meese et al.

(10) **Patent No.: US 6,713,464 B1**
(45) **Date of Patent: Mar. 30, 2004**

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

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(2), (4) Date: **Jan. 2, 2001**

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PCT Pub. Date: **Nov. 18, 1999**

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(52) **U.S. Cl.** **514/175**; 514/529; 514/530; 514/546; 514/547; 514/548; 549/269; 560/140; 560/255; 564/316

(58) **Field of Search** 560/110, 108, 560/121, 123, 124, 138, 140, 142, 255; 514/530, 531, 532, 533, 534, 544, 547, 548, 551, 175, 529; 549/269; 564/316

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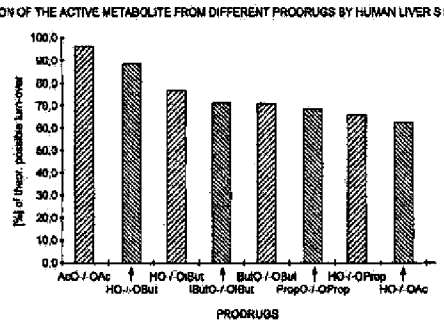
Assistant Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Edwards & Angell, LLP; Peter F. Corless; Christine C. O'Day

(57) **ABSTRACT**

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 relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, 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.

26 Claims, 1 Drawing Sheet



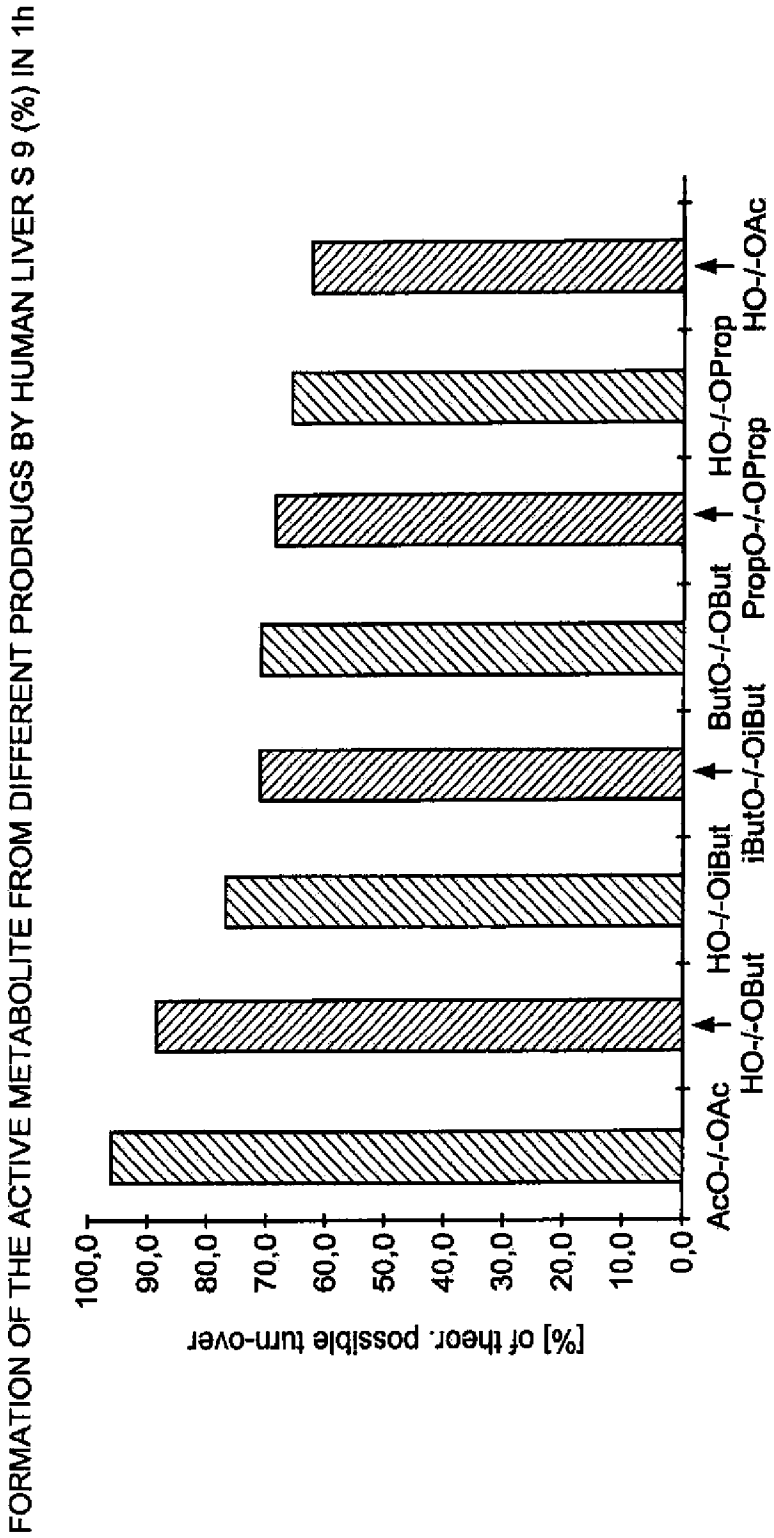

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
AcO-/-OAc
HO-/-OBut
HO-/-OiBut
iButO-/-OiBut
ButO-/-OBut
PropO-/-OProp
HO-/-OProp
HO-/-OAc
PRODRUGS

FIG. 1

DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

BACKGROUND OF THE INVENTION

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.

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.

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).

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.

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.

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.

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.

SUMMARY OF THE INVENTION

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.

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.

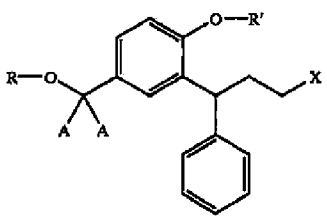
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the formation of the active metabolite from different prodrugs by human liver S 9(%) in 1 hour.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, novel 3,3-diphenylpropyl amines are provided, which are represented by the general formulae I and VII

Formula I



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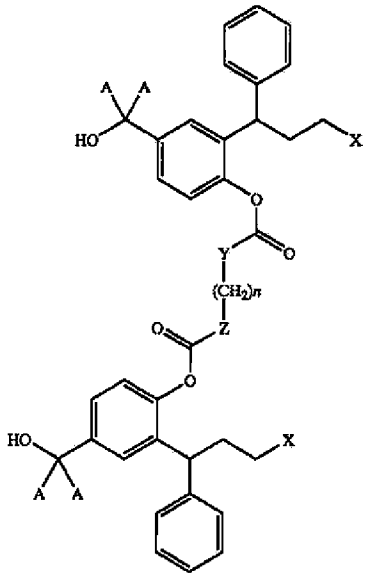
Formula VII'



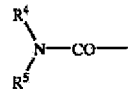
wherein R and R' are independently selected from

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

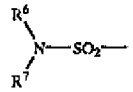
c) C_1–C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

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,

X represents a tertiary amino group of formula Ia

Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocaryl 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.

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, hydrobromide and the like.

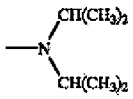
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

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_{1-5}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

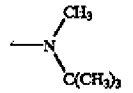
According to another embodiment of the invention, at least one of $R^{8\ and\ R9}$ comprises a branched carbon chain.

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

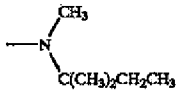
a)



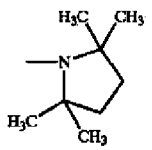
b)



c)



d)



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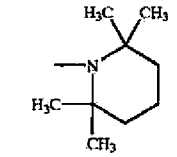
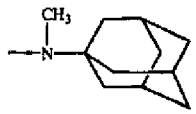
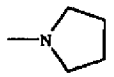


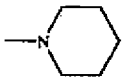
e)



f)



g)



h)

Group a) is particularly preferred.

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.

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.

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, nitro and the like. 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.

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.

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

The term "benzoyl" denotes an acyl group of the formula —CO—C_6H_5 wherein the phenyl ring may have one or more substituents.

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.

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.

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.

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

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.

The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

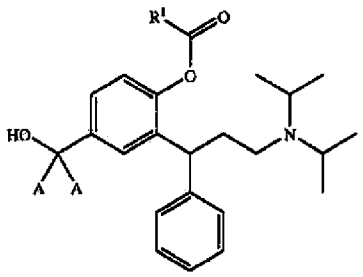
The term "Bn" as used herein denotes a benzyl group.

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

Preferred compounds according to the present invention are:

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

Formula II



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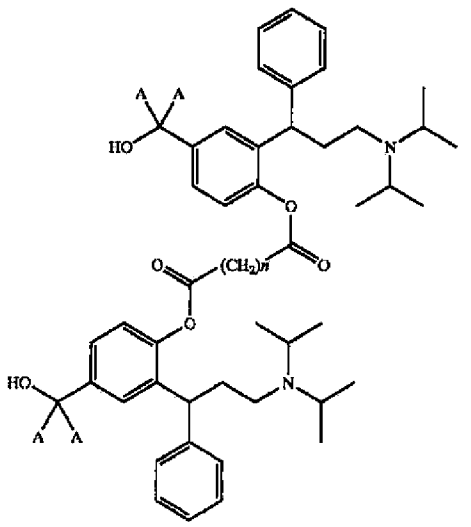
Formula II'



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-diisopropylamino-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,

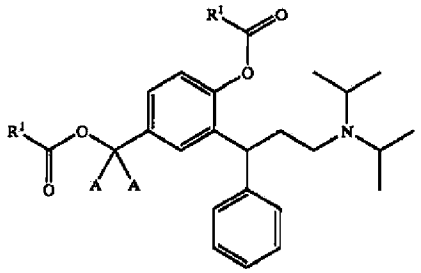
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-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

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,

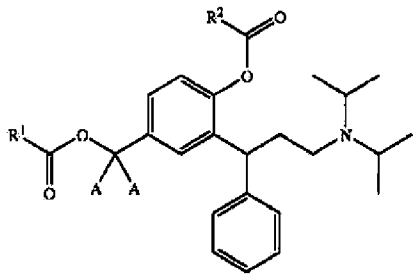
cyclic oct-4-ene-1,8-dioate of Intermediate B,

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 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,

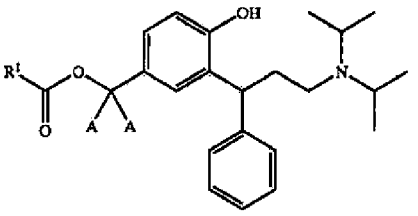
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-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,

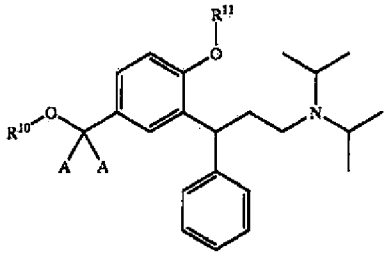
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-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-trimehylsilanyloxyphenyl)-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,

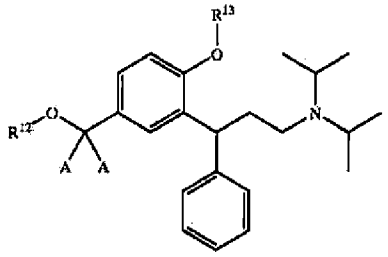
(±)-benzoic acid 4-benzyloxy-3-(3-d4isopropylamino-1-phenylpropyl)-benzyl ester,

(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

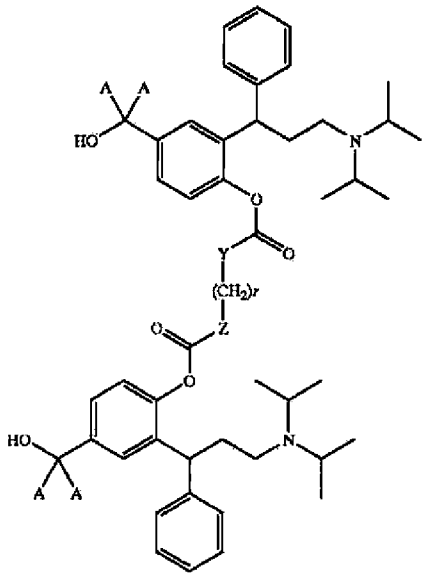
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

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

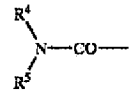
Formula VII



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 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,

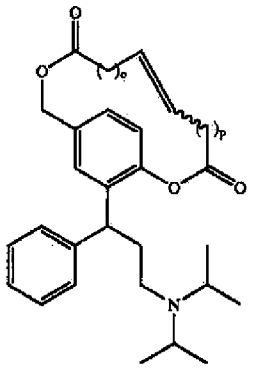
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'

Formula IX



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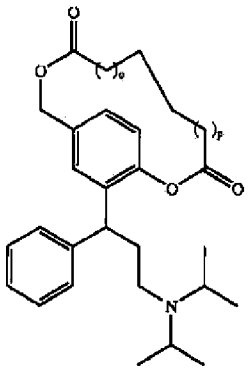
Formula IX'

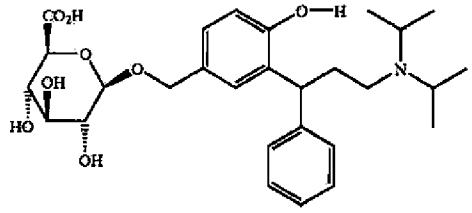


wherein o and p are the same or different and represent the number of methylene units $-(CH_2)-$ and may range from 0 to 6,

(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



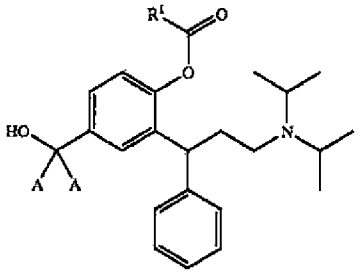
and

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.

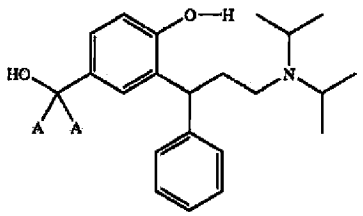
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, he following processes are provided:

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

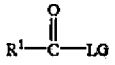
Formula II



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

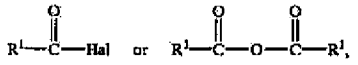


with an equivalent of an acylating agent selected from



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.

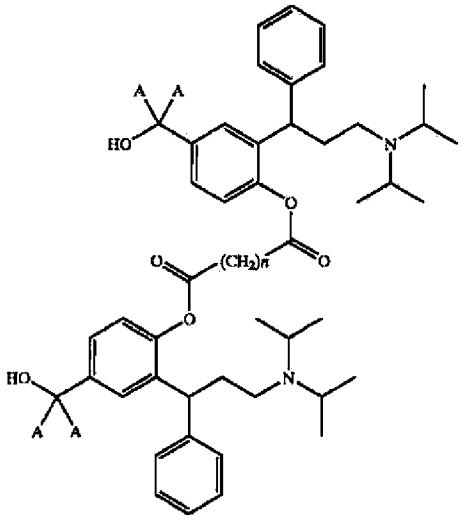
Preferably, the acylating agent is selected from



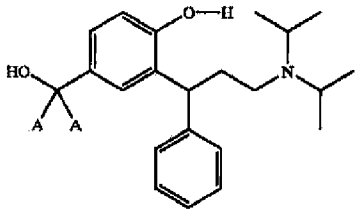
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is a defined above.

A process for the production of phenolic monoesters represented by the general formula I'

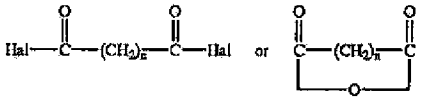
Formula II'



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

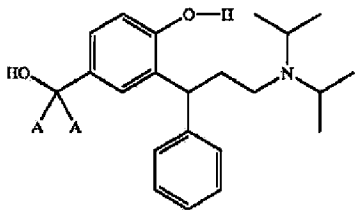


with an acylating agent selected from



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

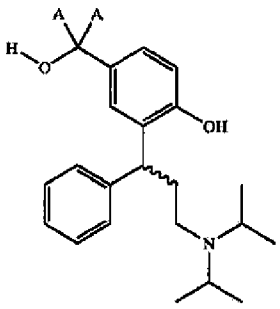
Hence, in these processes, an Intermediate B having the formula



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.

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



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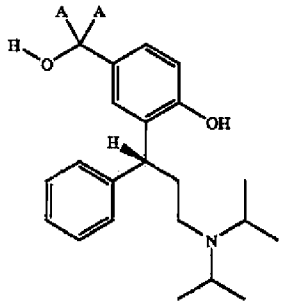
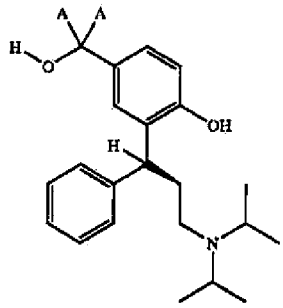
Intermediate R-(+)



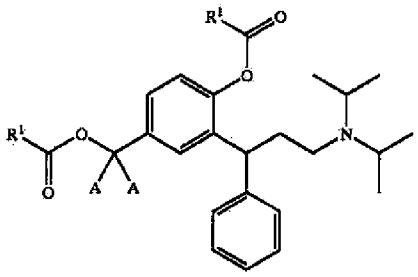
Intermediate S-(-)



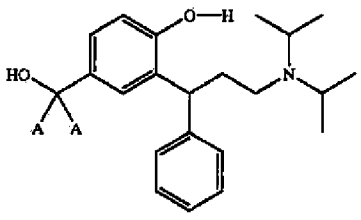
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III

Formula III

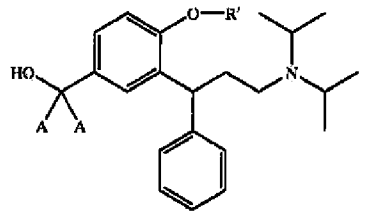


as defined above can be prepared by a process which comprises treatment of a compound of the formula



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

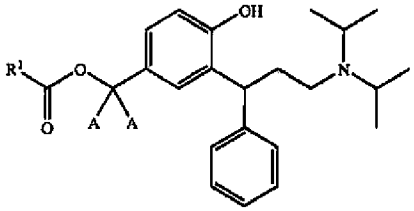
Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In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



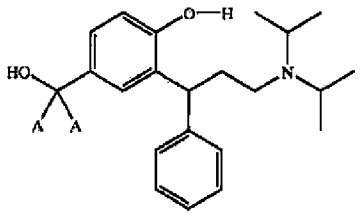
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes 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

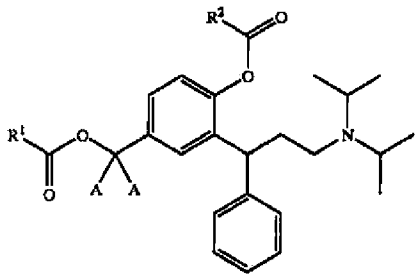


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

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.

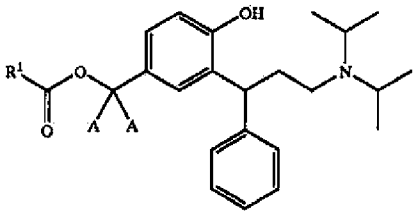
The mixed diesters represented by the general formula IV

Formula IV



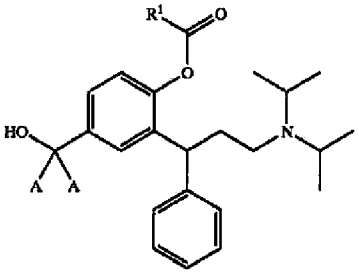
wherein R^1 and R^2 are as defined above can be precared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V

Formula V



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

Formula II

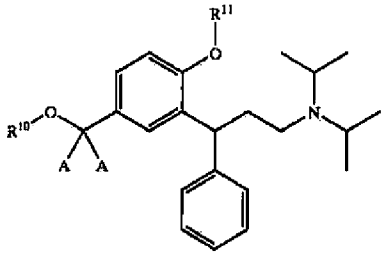


as defined hereinbefore.

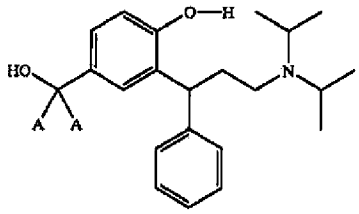
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI

Formula VI



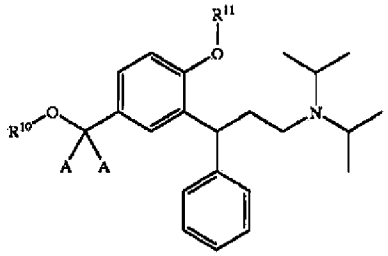
as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



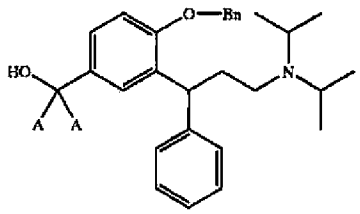
with an alcohol R^{10}—OH in the presence of an esterification catalyst.

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

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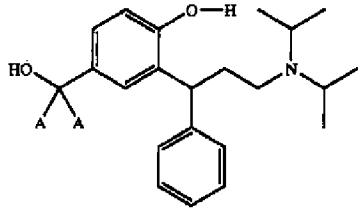
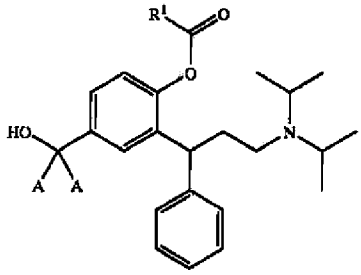


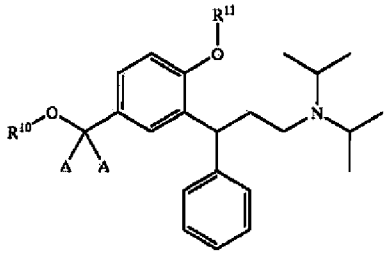
and

Formula II



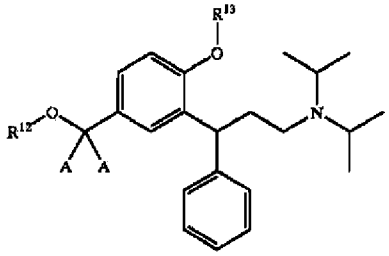
or

Formula VI

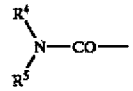


wherein R^{10} is hydrogen and R^{11} is as defined above or

Formula VII



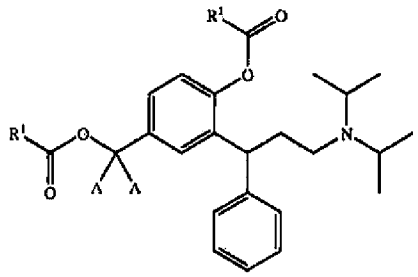
wherein R^{12} is hydrogen and R^{13} represents a C_1–C_6 alkoxycarbonyl group or



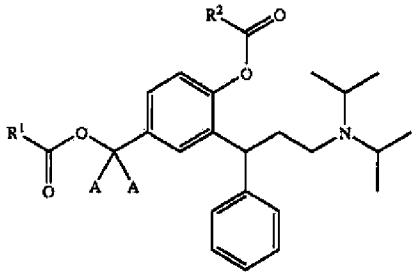
wherein R^4 and R^5 are as defined above

or of benzylic acylates selected from

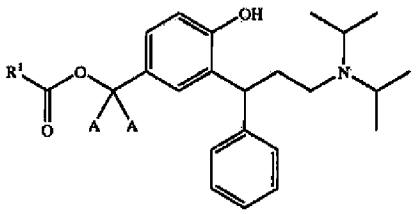
Formula III



Formula IV

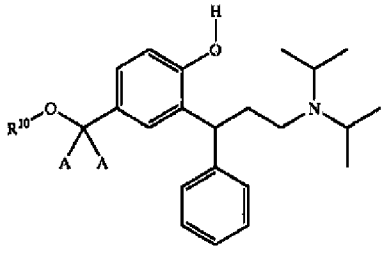


Formula V



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

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



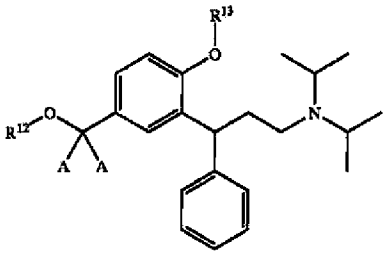
wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

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]).

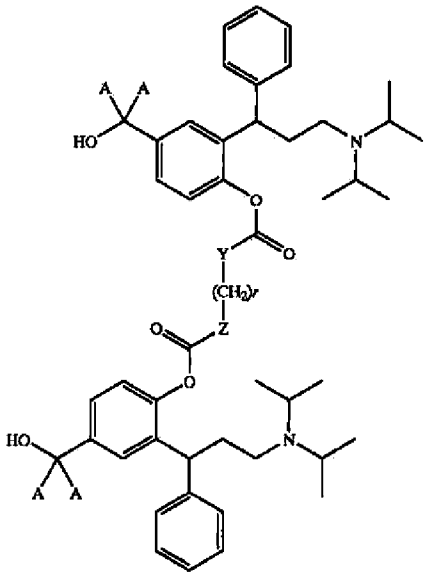
Likewise the phenolic hydroxy groups are readily transformed into phenyl ethers (R^{13}=alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis 1981, 1–28). Similarly, both phenolic and alcoholic monosilyl 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. Thuriéau, J.-L. Fauchère, Helv. Chim. Acta 76: 2465–2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. 26: 4307–4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

Formula VII

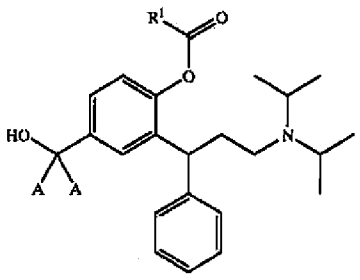


Formula VIII

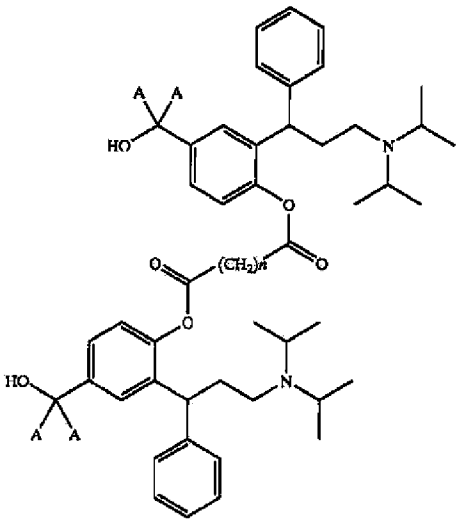


as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of

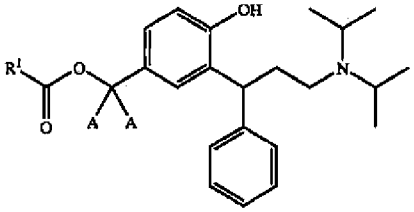
Formula II



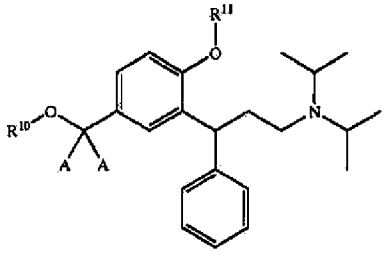
Formula II'



Formula V



Formula VI



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

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.

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.

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

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, for nasal spray administration or the like, in accordance with accepted pharmaceutical 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 phosphae, 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, flavouring agents, buffers, and the like.

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, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

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.

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.

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

1. Experimental

1. General

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). Thin-layer chromatography (tlc, R_f val-

ues reported) was conducted on precoated 5×10 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

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

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 ethylacetate. 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

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 (2×300 ml) and the extract was washed with water (2×200 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

A solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic 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%.

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

Warm solutions of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic 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 or 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 7S,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.

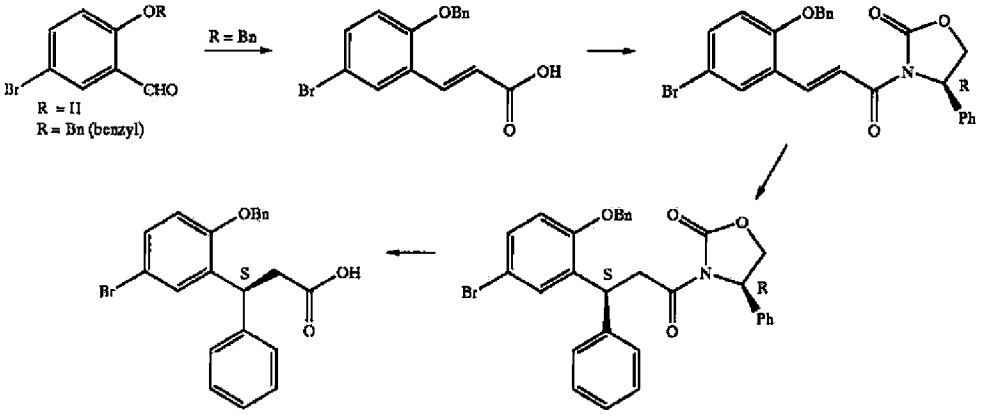
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 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 racemtic acid.

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

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 redissolved in dichloromethane (1.5 liter) 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.

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



2-Benzyloxy-5-bromobenzaldehyde

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-bromo-benzaldehyde was used as such in the next step.

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

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

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

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

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.

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

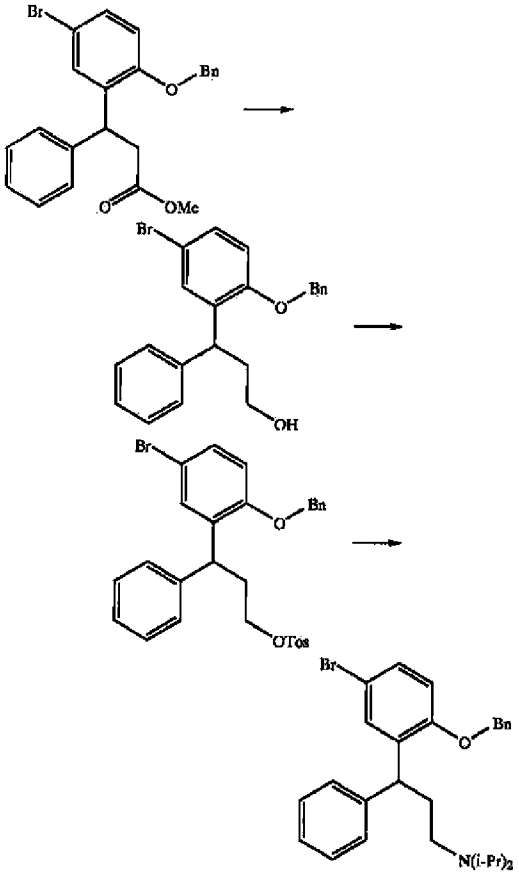
"nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(−)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ =+21.6 (c=0.5, MeOH).

R-(−)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

Conjugate organocuprate addition of phenylmagnesium-bromide 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-benzyloxy-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



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

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 aluminium hydride (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.

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.

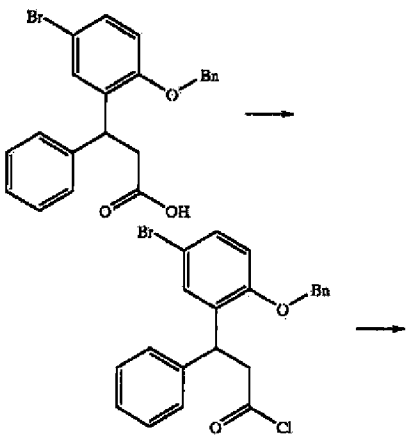
(±)-Toluene-4-sulphonic Acid 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl Ester

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

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



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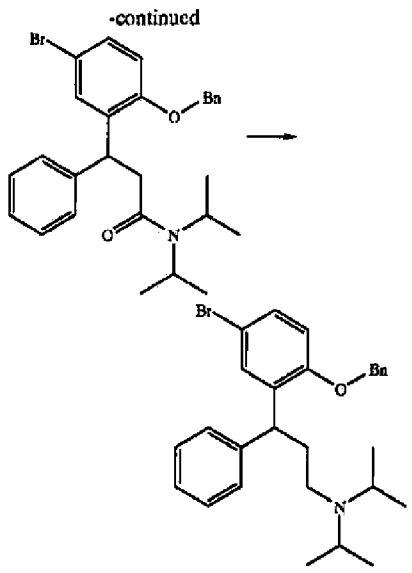


S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl Chloride

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 g). 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

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, 69.61.

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

The amide was prepared from duisopropylamine 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

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/tetrahydrofuran (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-(+)-13-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

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

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%.

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

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic Acid Hydrochloride

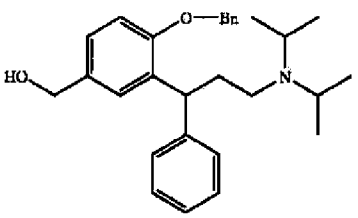
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to −60° C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and 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)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6 h 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 (2 h) 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)

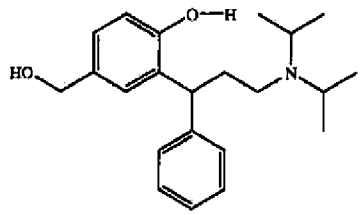
Repetition of the above described reduction of the methylester of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centered 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)

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-diisopropylamino-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

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

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. R-(+)-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

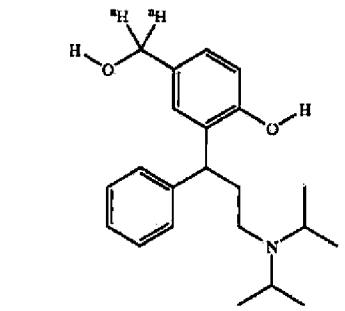
Intermediate d_2-B (n=2)

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 centered 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, 144.80, 155.52.

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 (2x5 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

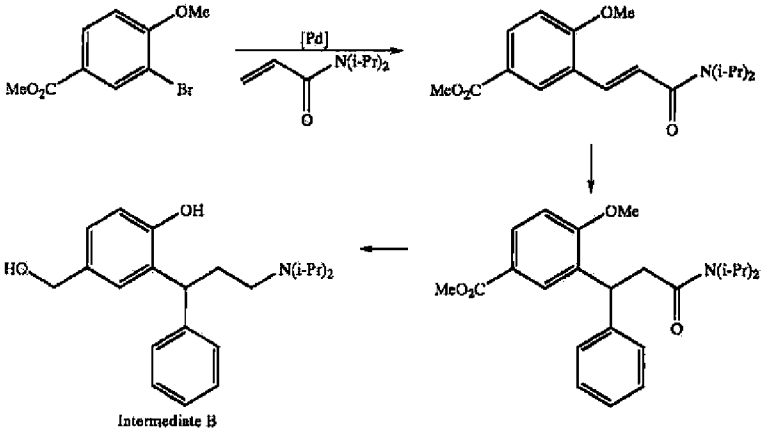


n = 2, deuterium

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

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



N,N-Diisopropyl-acrylamide

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 (3×100 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)

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)

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^+, 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

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

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.

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).

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. Example

a) Phenolic Monoesters

aa) General Procedure

Esters of Carboxylic Acids

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

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)

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).

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 3 (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 3 (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, 164.99.

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, 127.8, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 34.27, 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^+, 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^+, 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^+, 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-7-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, 121.80, 136.99, 138.94, 143.82, 147.65, 168.72.

b) Identical Diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine 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.

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

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.

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, 128.39, 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

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 9) 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.

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 (CD)CO_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

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.

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:

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.

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

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, 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, 129.42, 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, triethylsilyl 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-isopronoxymethylphenol, 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. 140.400, tlc (4) 0.61. LC-MS: 383 (6%, [M-HCl]+), 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

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 diisocyanaze (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

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.

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:

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.

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

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-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-phenyl-propyl)-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, 36.98, 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.

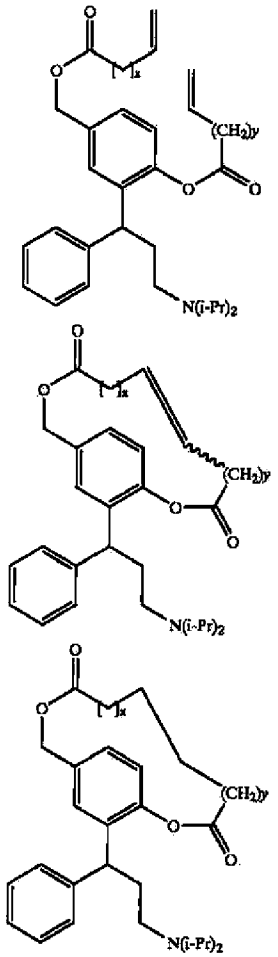
(±)-{4-C2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

(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)



Example:

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

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-diisopropyl amino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 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 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 an vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-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.

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

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

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 15 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 B 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

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 described 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 or 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5° C.

NMR Analysis

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 ($\underline{CH_3}$), 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 $\underline{CH}$).

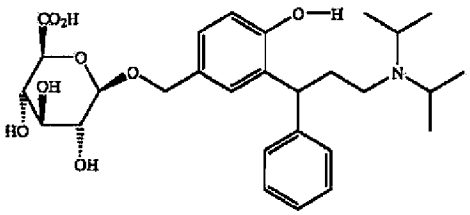
h) Inorganic Ester

Example:

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

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)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (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 filtrae 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 cave (±)-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, 20.51, 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.

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

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.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, Mass., USA.

In a routine assay, 25 μL of pooled human liver S 9 (20 mg protein/mL, H961, Gentest, Woburn, Mass., 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.

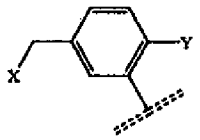
The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in FIG. 1.

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:

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
Prepo-/-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

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.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

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%.

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

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 a 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

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.

The compounds were tested for their anticholineruic 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) contractile 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

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

Different compounds of the invention were tested or 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 oft the invention are summarized in the following table.

Penetration through human skin

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

Disubstitution 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.

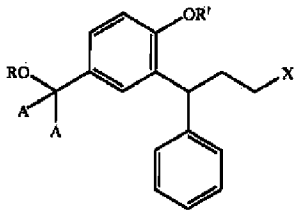
Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S 9 preparation.

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

What is claimed is:

1. A 3,3-Diphenylpropylamine of the general formula I:

Formula I



wherein R and R' are independently

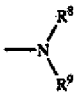
a) hydrogen; or

b) formyl, C_1–C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstitited arylcarbonyl;

with the proviso that R' is not hydrogen, methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia

Formula Ia

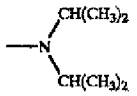


wherein R^8 and R^9 represent C_1–C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

A represents hydrogen (^1H) or deuterium (^2H), and

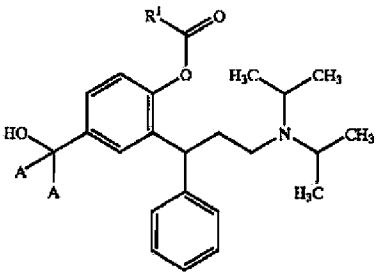
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

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

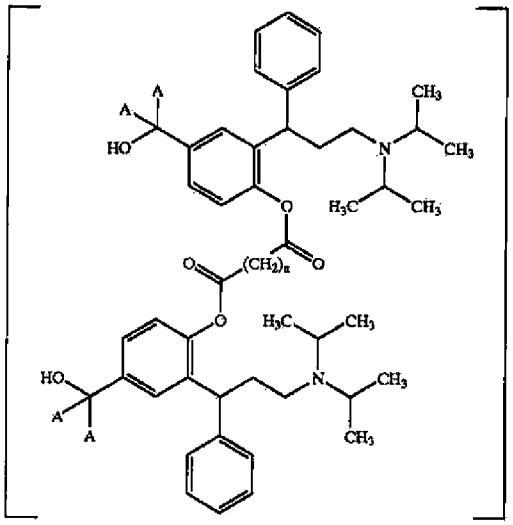


3. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from phenolic monoesters represented by the general formula II

Formula II



Formula II'



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

4. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from:

(±)-formic acid 2-(3diisopropylamino-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,

(±)-2,2methylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-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)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,

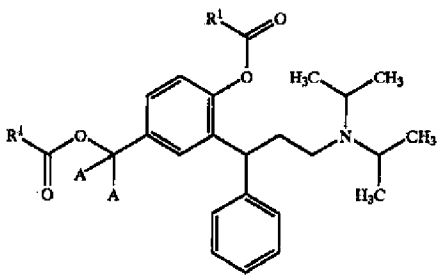
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

5. The 3,3-Diphenylpropylamine as claimed in claim 2 represented by the general formula III

Formula III



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl.

6. The 3,3-Diphenylpropylamine 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-dimethylpropionyloxy)-benzyl ester,

(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

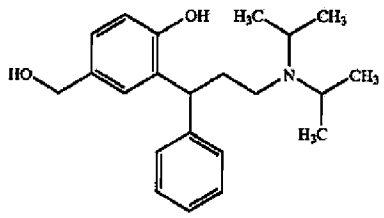
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-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,

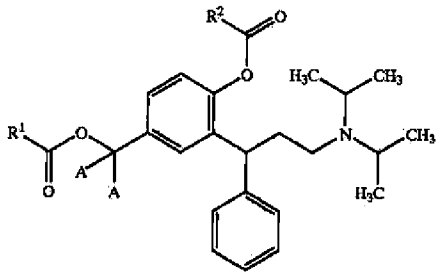
cyclic octane-1,8-dioate of Intermediate B, and

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



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

Formula IV



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl, 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. The 3,3-Diphenylpropylamine 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,

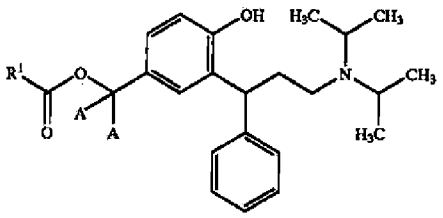
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, and

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

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

Formula V



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl.

10. The 3,3-Diphenylpropylamine 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,

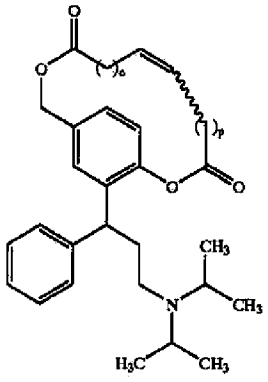
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, and

(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. A 3,3-Diphenylpropylamine selected from

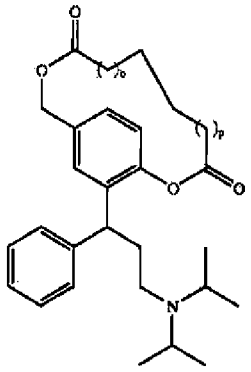
(i) compounds of the formulae IX and IX'

Formula IX



-continued

Formula IX'

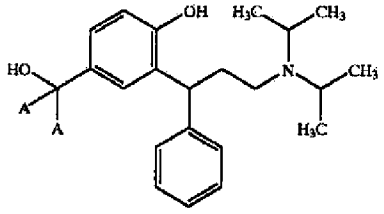


wherein o and p are the same or different and range from 0 to 6,

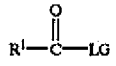
(ii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethylphenol and

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

12. A process for the production of phenolic monoesters according to claim 3, which comprises treatment of a compound of the formula

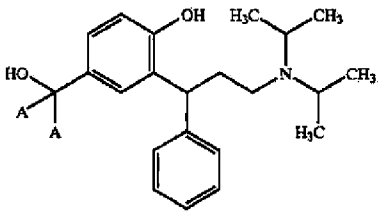


with an equivalent of an acylating agent of formula

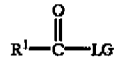


wherein LG represents a leaving group selected from halide, carboxylate and imidazolide in an inert solvent in the presence of a condensing agent.

13. A process for the production of identical diesters according to claim 5, which comprises treatment of a compound of the formula

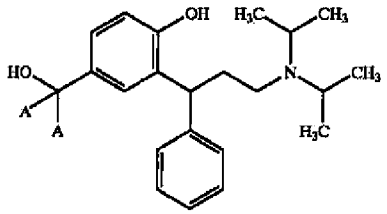


with at least two equivalents of the acylating agent of formula



wherein LG represents a leaving group selected from halide, carboxylate and imidazolide in an inert solvent in the presence of a condensing agent.

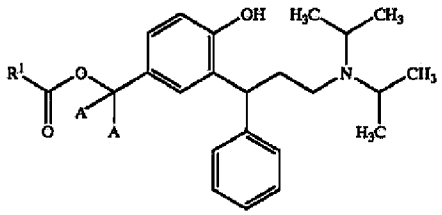
14. A process for the preparation of benzylic monoesters according to claim 9, which comprises treatment of a compound of the formula



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

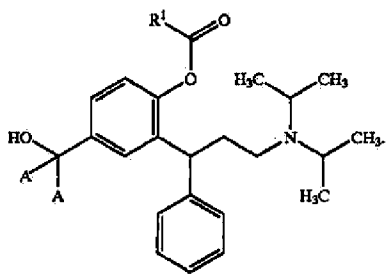
15. A process for the preparation of mixed diesters according to claim 7, which comprises acylation of a benzylic monoester represented by the general formula V

Formula V



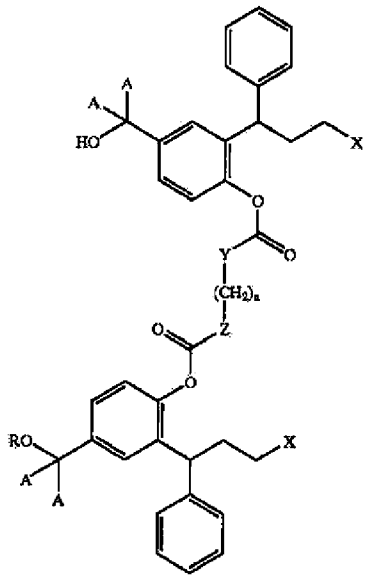
or of a phenolic monoester represented by the formula II

Formula II



16. A 3,3-Diphenylpropylamine of the general formula VII':

Formula VII'



wherein R is

a) hydrogen; or

b) formyl, C_1–C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl;

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,

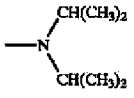
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12, and

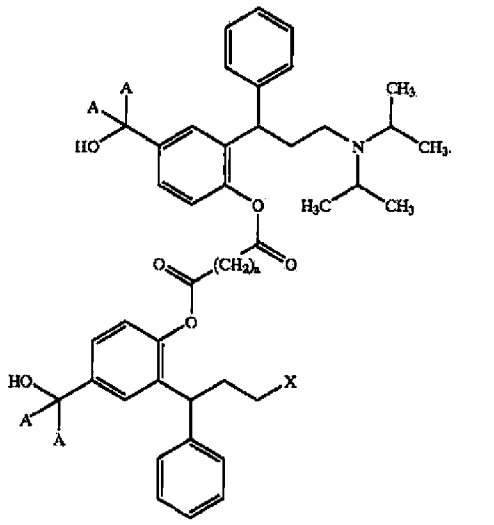
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

17. The 3,3-Diphenylpropylamines as claimed in claim 16, wherein X is

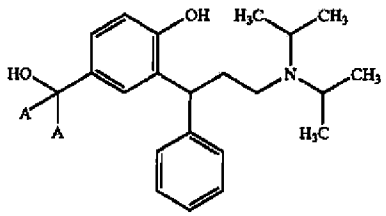


18. The 3,3-Diphenylpropylamine as claimed in claim 17, selected from phenolic monoesters represented by the general formula II'

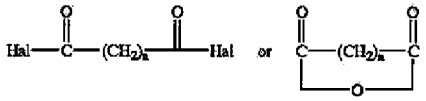
Formula II'



19. A process for the production of phenolic monoesters according to claim 18, which comprises treatment of two equivalents of a compound of the formula



with an acylating agent of formula



wherein Hal represents a halogen atom.

20. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1–10, 11 and 16–18 and a pharmaceutically acceptable carrier.

21. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 1–10, 11 and 16–18.

22. A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim 20 effective to diminish or eliminate symptoms of the disease.

23. The method according to claim 22 wherein the disease is urinary incontinence.

24. The method according to claim 23 wherein the mammal is a human.

25. A 3,3-Diphenylpropylamine selected from:

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]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, and

(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester.

26. The 3,3-Diphenylpropylamine of claim 2, wherein the 3,3-Diphenylpropylamine is R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 9, delete "hydrocaryl" and insert therefor -- hydrocarbyl --.
Line 43, delete "$R^{8 \text{ and } R9}$" and insert therefore -- R^8 and R^9 --.

Column 8,
Line 21, after "formula" add -- III --.

Column 9,
Line 18, delete "R" and insert therefor -- R^2 --.

Column 10,
Line 49, delete "2-trimehylsilanyl" and insert therefor -- 2-trimethylsilanyl --.

Column 11,
Line 9, delete "3-d4isopropyl" and insert therefor -- 3-diisopropyl --.

Column 13,
Line 47, delete "he" and insert therefor -- the --.

Column 14,
Line 38, after "formula" delete "I'" and insert therefor -- II' --.

Column 17,
Line 64, delete "can, be" and insert therefor -- can be --.

Column 18,
Line 23, delete "precared" and insert therefor -- prepared --.

Column 24,
Line 31, delete "phosphae" and insert therefor -- phosphate --.

Column 26,
Line 49, delete "7S,2R" and insert therefor -- 1S,2R --.

Column 31,
Line 53, delete "69.61" and insert therefore -- 169.61 --.
Line 56, delete "duisopropylamine" and insert therefor -- diisopropylamine --.

Column 32,
Line 11, delete "13-(2" insert -- [3-(2 --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 34,
Line 21, delete "R-(+)" and insert therefor -- S-(+) --.

Column 38,
Line 4, delete "Eaters" and insert therefor -- Esters --.

Column 39,
Lines 47 and 55, delete "Intermediate B 3 (0.50)" and insert therefor -- Intermediate B (0.50) --.

Column 40,
Line 6, delete "127.8" and insert therefor -- 127.58 --.
Line 8, delete "34.27" and insert therefor -- 134.27 --.
Line 62, delete "Diisopropylamino-7-phenyl" and insert therefor -- Diisopropylamino-l-phenyl --.

Column 41,
Line 61, delete "121.80" and insert therefor -- 131.80 --.

Column 45,
Line 11, delete "isopronoxymethylphenol" and insert therefor -- isopropoxymethylphenol --.
Line 14, delete "140.400" and insert therefor -- 140.4 °C --.
Line 44, delete "diisocyanaze" and insert therefor -- diisocyanate --.

Column 47,
Line 30, delete "amino)acetic" and insert therefor -- amino]acetic --.
Line 53, delete "4-C2-" and insert therefor -- 4-[2- --.

Column 51,
Line 4, delete "cave" and insert therefor -- gave --.
Line 53, delete "perchioric" and insert therefor -- perchloric --.

Column 52,
Line 21, delete "Propo-/" and insert therefor -- PropO-/ --
Line 54, delete "receptors" and insert therefor -- receptors. --

Column 53,
Line 56, delete "tested or" and insert therefor -- tested for --.
Line 66, delete "oft he" and insert therefor -- of the --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

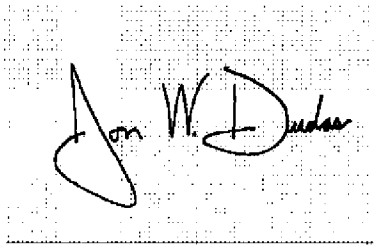
Column 55,
Lines 25-48, delete formula II.
Line 53, delete "3diisopropyl" and insert therefor -- 3-diisopropyl --.
Line 66, delete "2,2-methylpropionic" and insert therefor
-- 2,2-dimethylpropionic --.

Column 56,
Line 13, delete "propyl)hydroxyl" and insert therefor -- propyl)-4-hydroxy --.

Column 57,
Lines 54-58, insert a line break before the compound "R-(+)- benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester".

Signed and Sealed this

Thirty-first Day of May, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT G

US006858650B1

(12) **United States Patent**
Meese

(10) **Patent No.: US 6,858,650 B1**
(45) **Date of Patent: Feb. 22, 2005**

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

(75) Inventor: **Claus Meese**, Monheim (DE)

(73) Assignee: **Schwarz Pharma AG** (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/130,214**

(22) PCT Filed: **Nov. 15, 2000**

(86) PCT No.: **PCT/EP00/11309**

§ 371 (c)(1),
(2), (4) Date: **May 14, 2002**

(87) PCT Pub. No.: **WO01/35957**

PCT Pub. Date: **May 25, 2001**

(30) **Foreign Application Priority Data**

Nov. 16, 1999 (DE) 199 55 190

(51) **Int. Cl.**[7] **A01N 37/08**; A01N 37/12; A01N 37/44; A61K 31/215; A61N 31/24

(52) **U.S. Cl.** **514/530**; 514/531; 514/534; 514/548; 514/551; 560/61; 560/122; 560/123; 560/124; 560/138; 560/142; 560/250; 564/319

(58) **Field of Search** 514/530, 531, 514/534, 548, 551; 560/61, 122, 123, 124, 138, 142, 250, 37, 18, 42, 140; 564/319

(56) **References Cited**

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Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU–200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology. vol. 81, pp. 169–172 (1997).*

L. Palmer, L. Andersson, T. Andersson, U. Stenberg: *Determination of tolterodine and the 5–hydroxymethly metabolite in plasma, serum and urine using gas chromatography–mass spectrometry; Journal of Pharmaceutical and Biomedical Analysis*; Jan. 20, 1997; pp. 155–165.

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Primary Examiner—Richard L. Raymond
Assistant Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Peter F. Corless; Christine C. O'Day; Edwards & Angell, LLP

(57) **ABSTRACT**

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the manufacture and highly pure, stable intermediate products.

The method is in particular characterized by regio- and chemoselectivity and high yield. Salts of phenolic monoesters of 3,3-diphenylpropylamines are provided, that are particularly well-suited for use in pharmaceutical formulations. Preferred compounds are R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate. Furthermore, stable, crystalline intermediate products that are essential for obtaining the abovementioned salts are provided. A preferred intermediate product is R-(–)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester.

24 Claims, 1 Drawing Sheet

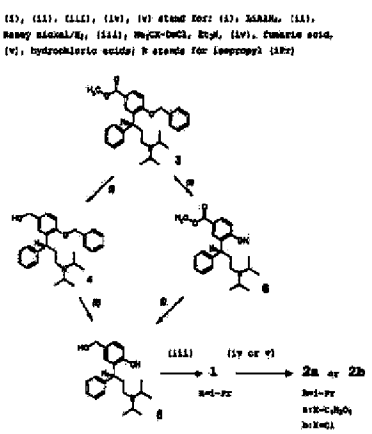
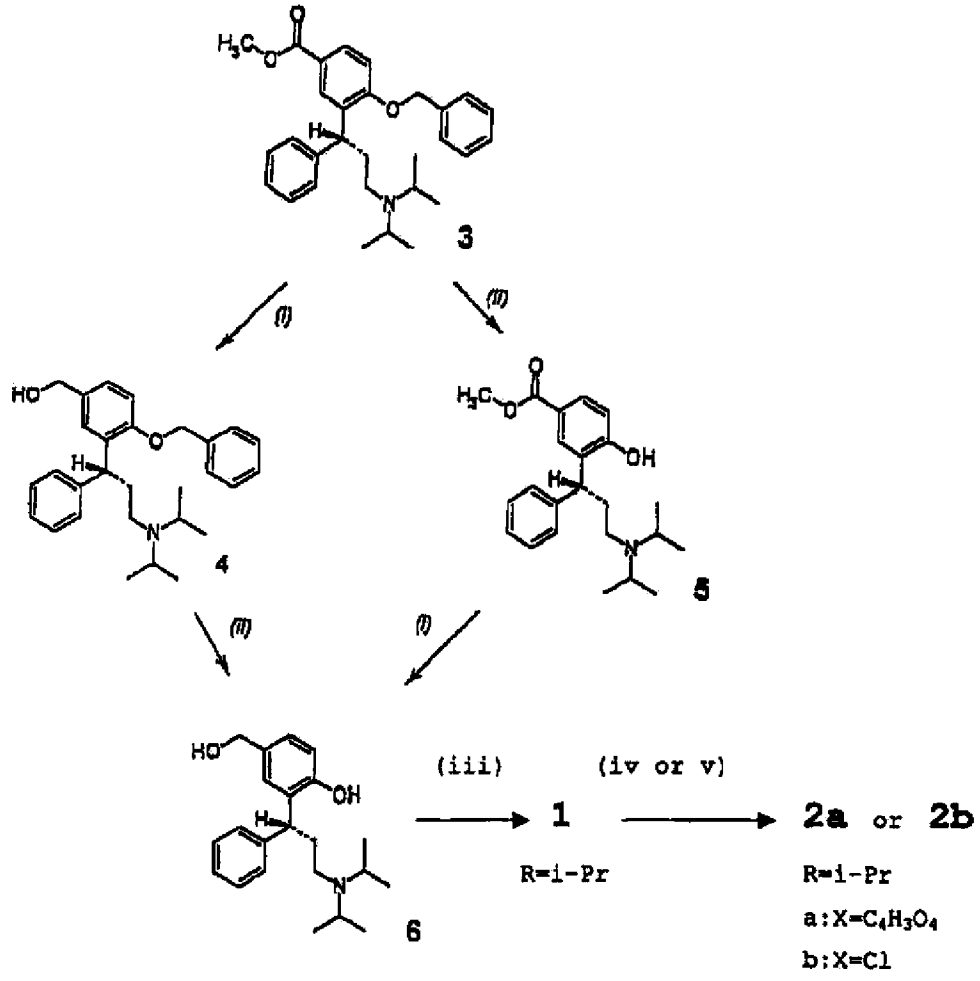


Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

This application was filed under 35 U.S.C. 371, and is the U.S. National Stage of PCT/EP00/11309, filed 5 Nov. 2000.

This patent application claims the benefit of priority under 35 U.S.C. §119 of German Patent Application No. 199 55 190.1, filed Nov. 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

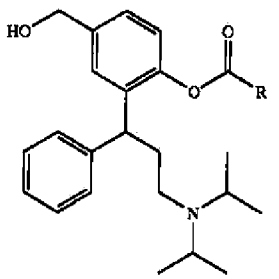
From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugn for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourale metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylarines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below

Formula A



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

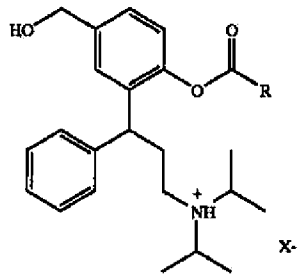
Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification. During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

Basically salts of the compounds of general formula A can be obtained if solutions of the compounds of formula A (base component) are purified with solutions of acids in suitable solvents, but the salts obtained in the form of solid matter can prove to be altogether amorphous and/or hygroscopic and cannot be directly crystallized from the normal solvents either. Such salts have inadequate chemical stability to be galenically processed as valuable pharmaceutically active substances.

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been prepared under a special reaction process, are converted with a physiologically compatible inorganic or organic acid with

general formula H-X, in which ^-X represents the respective acid residue, into their respective salt with general formula I.

Formula I



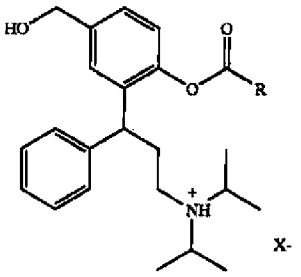
The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

A further problem for the present invention is to provide a method for manufacturing such highly pure, crystalline, stable compounds in the form of their salts, as well as highly pure, stable intermediate products.

The final problem for the invention is to provide a method for manufacturing the abovementioned compounds with which a high yield of the products of the process and the respective intermediate products can be obtained chemo- or regioselectively.

This problem is solved in that highly pure, crystalline, stable compounds of the 3,3-diphenylpropylamines in the form of their salts with general formula I are provided,

Formula I



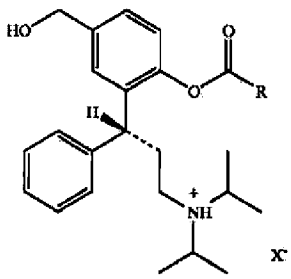
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with a design of the invention the salts of general formula I can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-acetylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

In accordance with a further design form of the invention R-configured compounds with general formula 2 are provided

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with an advantageous design form of the invention the compounds in the form of their salts of general formula 2 can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-acetylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and

R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Furthermore, compounds are preferred in which R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclo-propyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X denotes chloride.

Particular preference is for [(R)-3-(2-{1-[4-(1-cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl}-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride and {(R)-3-[2-(1-cyclohexyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride.

In the compounds of the present invention the expression "alkyl" preferably stands for a straight-chain or branched-chain hydrogen group with between 1 and 6 C-atoms. Special preference is for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The expression "cycloalkyl" designates cyclical hydrogen groups, that have between 3 and 10 hydrogen atoms, that may also contain suitable substitutes in place of the hydrogen atoms.

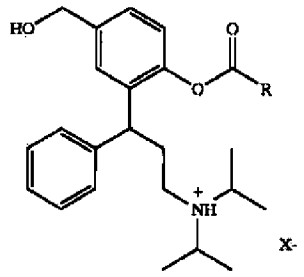
The expression "phenyl" designates a —C_6H_5-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable halogens are fluorine, chlorine, bromine and iodine atoms

The present invention also includes methods for manufacturing the compounds in accordance with the invention of general formula I as well as valuable intermediate products.

The method is characterised by chemo- and regioselectivity.

Compounds of General Formula I

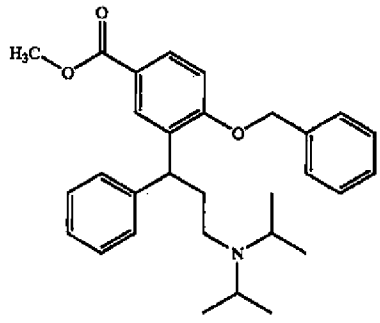
Formula I



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are that

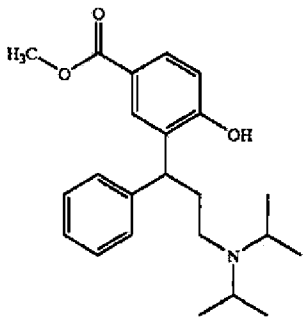
a) a compound of formula III

Formula III



is split with a hydrogenation agent to form a compound of formula V

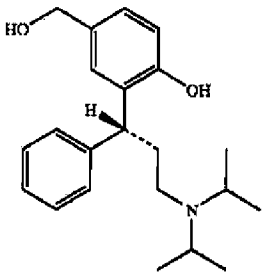
Formula V



whereupon

b) the compound of formula V so obtained is converted with agent, in order to give a compound of formula VI

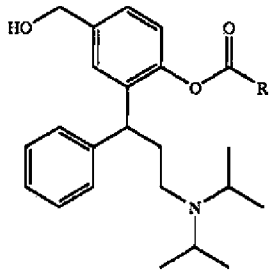
Formula VI



which

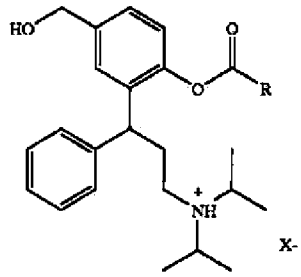
c) is converted with an acylation agent, in order to obtain of formula A

Formula A



in which R has the significance stated above, which d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

Formula I

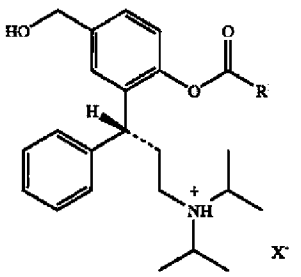


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with the invention, for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

In accordance with an advantageous further development of the invention a method for the manufacture of R-configured compounds of the general formula 2 is described,

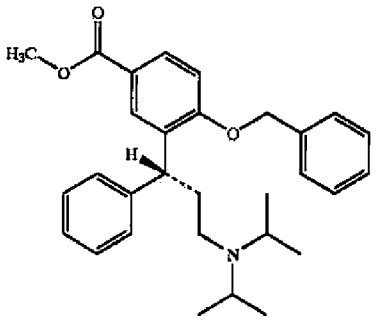
Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, in that

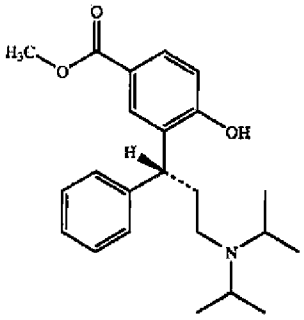
a) a compound of formula 3

Formula 3



is split with a hydrogenation agent to form a compound of formula 5

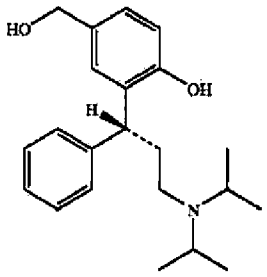
Formula 5



whereupon

b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6

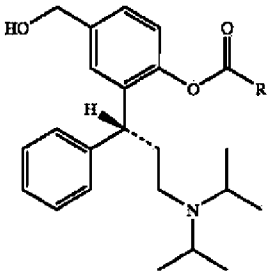
Formula 6



which

c) is converted with an acylation agent, in order to obtain a compound of formula 1

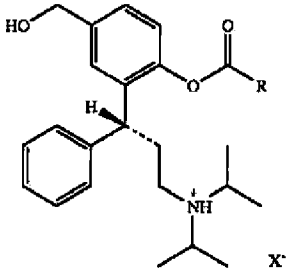
Formula 1



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2

Formula 2



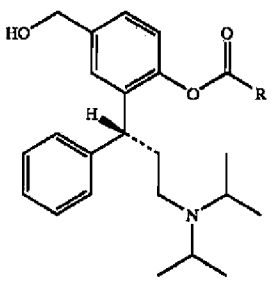
in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

Advantageously in order to obtain compounds of general formula 2, in accordance with the method hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(–)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(–)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Particular advantageously, on the basis of the crystalline R-(–)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzoic acid methyl ester, the highly pure, crystalline intermediate product R-(–)-3-(3-diisopropylamino-phenylpropyl)-4-hydroxy-benzoic acid methyl ester is prepared, which is reduced to R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, is finally acylated in a suitable manner and is then converted with a physiologically compatible inorganic or organic acid under spontaneous crystallization to the respective highly pure, crystalline, stable salt.

Depending on the acid chloride used, compounds of general formula 1 are obtained,

Formula 1



in which R denotes C_1–C_6-alkyl, in particular isopropyl, C_3–C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to obtain the compounds in accordance with the invention in the form of their salts the special reaction process via particular intermediate stages and individually identifiable intermediate products is crucial.

This is explained using reaction diagram 1 (see FIG. 1), in which the conversions with R-configured compounds are described, but without this being restrictive.

In this:

3=R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methyl ester

4=R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5=R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

6=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester

2a=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrogen fumarate

2b=R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate

In accordance with the reaction process explained in the embodiment the preliminary stage 3 (R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methylester) is prepared in crystalline, pure form.

Using normal methods—such as BBr_3, $AlCl_3$—but preferably by means of hydrogen gas via Raney nickel in methanol as the solvent at room temperature (RT), preliminary stage 3 is split into 5 (R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methylester. This develops in highly pure, crystalline form (melting point 143.7° C.).

Finally, using a suitable reducing agent—such as $NaBH_4$/EtOH—preferably $LiAlH_4$ 5 is reduced into an inert solvent at low temperature (−78° C. to +10° C.) and the compound 6 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) is obtained. The compound 6 is obtained in a highly pure state and can be crystallised from a suitable solvent such as ethyl acetate. The colourless, compact grained material has a melting point of 102.3° C. This is surprising in that the compound 6 in the state of the art is described as an amorphous solid.

Compound 6 is now acylated with very good yield and regio- and chemoselectivity, into a phenolic ester. This reaction is performed at RT or low temperatures with an equivalent acid chloride in the presence of a base in a suitable solvent. Suitable solvents are ethyl acetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene.

The reaction is preferably performed with isobutyrylchloride as the acid chloride and triethylamine as the base at the abovementioned temperatures. The 1 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester) then obtained, occurs with such purity that with solutions of the fumaric acid in suitable solvents spontaneous crystallisation starts with the formation of the hydrogen fumarate salt 2a.

This salt has a high melting point of 103° C., is stable at RT, is non-hygroscopic and does not contain crystallose agents. It can be recrystallised as often as desired.

If instead of fumaric acid anhydrous hydrochloric acid is used—for example as an etheric solution—salt formation also takes place with the crystalline product 2b (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate being obtained.

Following a further recrystallisation the product 2b has a melting point range of 97–106° C.

Finally the product 2b can particularly advantageously be obtained by the following variants of the inverse reaction process, starting with the compound 6 of reaction diagram 1. The product 2b can thus be obtained without the addition of an external acid-intercepting base, as explained in the following.

Solutions of 6 (R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) are dripped into solutions of isobutyrate chloride, so that under suitable polarity conditions the anhydrous product 2b rapidly crystallises out. 2b is very hygroscopic.

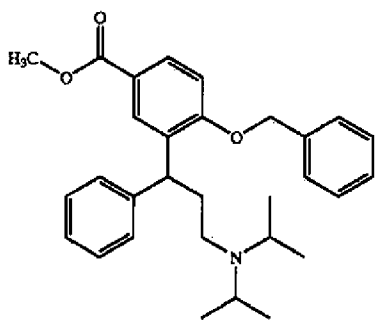
If the abovementioned reaction is carried out in a humid solvent, that contains at least one mole equivalent of water, a stable and crystalline, hydrate-containing product 2b is obtained, that has the abovementioned melting characteristics.

The compounds in accordance with the invention of general formulae 1 and 2 are suited to bulk material.

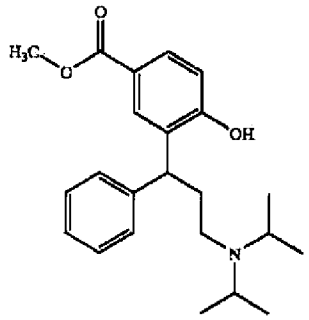
Of particular advantage are the highly pure compounds of general formulas III, V, VI, 3, 5, 6 and 7 which can be obtained.

Compound of Formula III

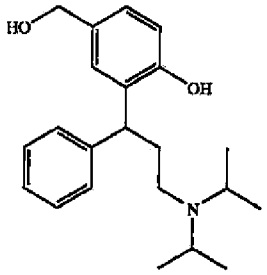
Formula III



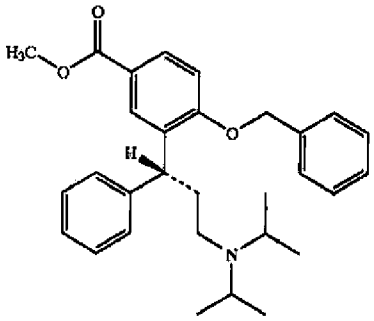
Compound of Formula V



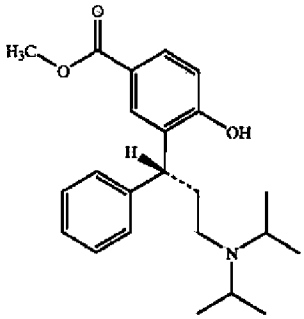
Compound of Formula VI



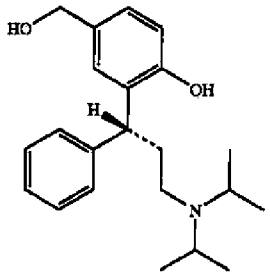
Compound of Formula 3



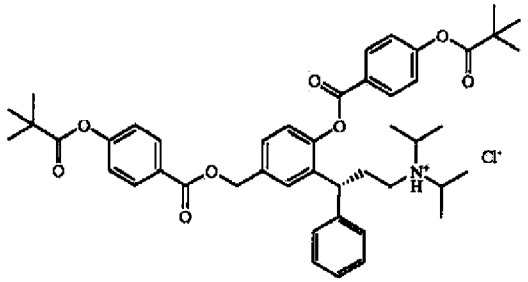
Compound of Formula 5



Compound of formula 6



Compound of Formula 7



[(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methane-oyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methane-oyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chloride.

The abovementioned compounds III, V, VI, 3, 5, 6 and 7 are particularly suited to use in each case as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

Of particular advantage are compounds for use as an intermediate product in the manufacture of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and R -(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Finally, the method can be carried out in a particularly advantageous way by converting a compound of general formula 6 (see reaction diagram 1) with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester.

In accordance with the invention R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is particularly suited to conversion with fumaric acid or hydrochloric acid with the formation of the respective salt.

The following embodiments explain the invention.

Experimental

I. General

All compounds have been fully characterised by ^1H and ^{13}C NMR-spectroscopy (Bruker DPX 200). The stated chemical displacements in the ^{13}C-NMR-spectra (50 MHz, ppm values stated) refer to the solvent resonances of $CDCl_3$ (77.10 ppm) ^1H NMR data ($CDCl_3$; 200 MHz, ppm) refer to internal tetramethylsilane).

Thin layer chromatography (DC, R_f given) was carried out on 5×10 cm E. Merck silica gel films (60F254), and the stains were revealed by fluorescence erasure or by spraying with alkaline potassium permanganate solution.

Absorbent systems were: (1), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%).

The optical rotations were measured at a wavelength of 589.3 nm (sodium D-line), at room temperature using ethanol as a solvent (apparatus: Perkin Elmer Polarimeter Type 241), melting points (in ° C.) are uncorrected and were determined on the Mettler FP apparatus, or by differential thermoanalysis (DSC) on the Perkin Elmer Model DSC7, using "Pyris" evaluation software.

UV/VIS measurements were carried out on the spectrophotometer. model Lambda 7 (Perkin-Elmer) with a layer thickness of 1 cm. The specific absorption stated is for a 1% solution ($A^{1\%}_{1\ cm}$)

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer Series 1610 (resolution 4 cm^{-1}).

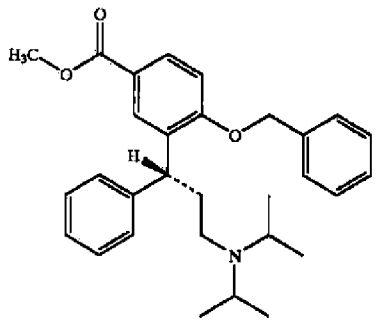
Gas chromatography mass spectrometry (GC-MS, m/z values and relative intensity with reference to the base ion (%) was carried out with a Finnigan TSQ 700 Triple Mass Spectrometer in positive (P-CI) or negative (N-CI) chemical ionization measurement mode with methane or ammonium as a reactant gas or via electron impact ionisation. Hydroxy compounds were measured as trimethylsilylether-derivatives.

Coupled liquid chromatography-mass spectrometry (LC-MS): Waters Integrity System, Thermabeam Mass Detector (EI, 70 eV), m/z-values and relative intensity (%) are given over a quantity range of 50–500 a.m.u.

II. Embodiments

The Arabic numerals in brackets (3), (4), (5), (6) refer to the identical designations in reaction diagram 1.

1. Preparation of R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl-ester (3)



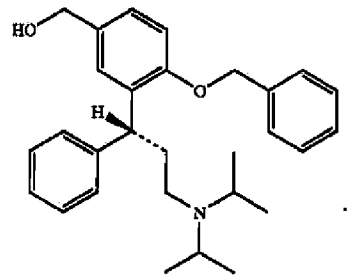
A solution of R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid hydrochloride (2.30 kg, 4.77 Mol) in 26.4 litres of methanol and 0.25 litre of concentrated sulphuric acid is heated for 16 hours with recycling. Then a third of the solvent is distilled off, cooled and under agitation mixed with 5 kg ice and 2.5 litres 25% aqueous sodium carbonate solution. The deposit is first extracted with 15 litres and then again with 5 litres of dichloromethane. The organic phases are purified and concentrated on the rotary evaporator until dry. 1.99 kg (90.7% of theoretical) dark yellow oil with a purity of approximately 90% (DC, NMR) are obtained.

DC (1): 0.58

^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.63, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22,129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Recrystallisation 69.0 oily raw material is dissolved in 150 ml boiling methanol. Following the addition of 15 ml distilled water it is left at 0° C., whereupon colourless crystals precipitate. These are filtered off, washed with a little cold methanol and vacuum-dried. Yield: 41.8 g (60.6% of theoretical) colourless crystals, melting point 89.8° C.; $[I]_D^{20}$=−30.7(c=1.0, ethanol).

2. Preparation of R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)

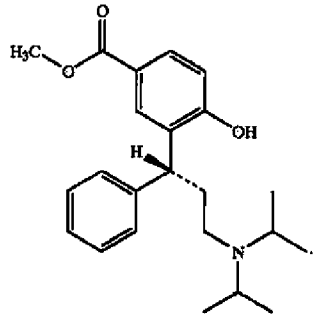


Raw product (3) (28 g) is dissolved in 230 ml pure diethylether and under agitation is dripped into a suspension of 1.8 g lithium-aluminium hydride in diethylether (140 ml). After 18 hours of agitation at room temperature, 4.7 ml of water are added in drop form. The organic phase is separated off, dried with anhydrous sodium sulphate, filtered and concentrated on the rotary evaporator until dry. 26 g (98.9% of theoretical) R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) are obtained as a colourless oil.

DC (2): 0.32; $[I]_D^{20}$=+6.3 (c=1.0, ethanol).

^{13}C-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.

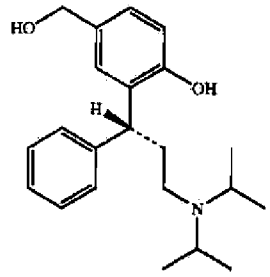
3. Preparation of R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5)



To an agitated suspension of 5 g Raney nickel (washed with water, then with methanol) in 200 ml methanol, 10 g (21.8 mmol) R-(−)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl ester (3) are added. Following brief heating, in order to dissolve all (3) completely, the apparatus is placed under a hydrogen gas atmosphere. After three hours of agitation at normal pressure and room temperature, the thin layer chromatography demonstrates complete conversion. The deposit is rinsed with nitrogen gas and following addition of some active charcoal is filtered. Following concentration of the methanolic solution on the rotary evaporator 6.0 g (75% of theoretical) R-(−)-3-(3-diisopropylaminophenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5) remains in the form of colourless crystals with a purity of 99.6% (HPLC).

Melting point 143.7° C.; DSC 144.7° C.
$[I]_D^{20}$=−26.6 (c=0.93, ethanol).
^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Preparation of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Starting from the intermediate stage (4), R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) are dissolved in 220 ml methanol and Raney nickel (5 g). The apparatus is rinsed with hydrogen gas and the deposit is agitated for two days at room temperature. Following the addition of a further 5 g Raney nickel, agitation for a further two days at room temperature takes place under a hydrogen gas atmosphere, followed by filtration off from the catalyser and concentration until dry on the rotary evaporator. The oily, pale yellow residue is dissolved in 100 ml diethylether, washed twice with 100 ml water each time, dried via sodium sulphate, filtered and concentrated until dry. 14.1 g (90.4% of theoretical) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol are obtained in the form of a cream-coloured, amorphous. solid. For recrystallisation see under c).

b) Starting from the intermediate stage (5); R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

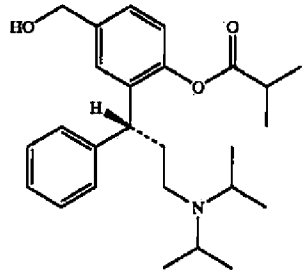
A solution of 370 mg (1.0 mmol) R-(−)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester in 20 ml anhydrous tetrahydrofurane is slowly and at room temperature dropped into an agitated mixture of dried tetrahydrofurane (10 ml) and a 1M solution of lithium-aluminium hydride in tetrahydrofurane (3 ml) (under a nitrogen protective gas atmosphere). Excess hydride is decomposed by the dropped addition of a saturated sodium carbonate solution. Following separation of the organic phase this is concentrated on the rotary evaporator and then dried in the high-vacuum. 274 mg (74% of theoretical) pale yellow oil is obtained, that slowly solidifies into an amorphous mass.

c) Recrystallisation

Raw product 6 (1.0 g) is dissolved in ethyl acetate and again concentrated on the rotary evaporator. The diol released in this way from foreign solvents (diethyl ether or tetrahydrofurane, see above) has 1.5 ml ethyl acetate added with slight heating. Agitation takes place until a clear solution results, followed by cooling at room temperature and addition of a few seed crystals. These are obtained by purifying raw 6 via HPLC, collecting the main fraction, concentrating this and drying the residue for a number of hours in the high-vacuum. Once clear crystallisation has definitely started, it is left at −10° C. The crystals are sucked off in the cold and dried in the vacuum. Colourless crystals with a yield of 84% are obtained.

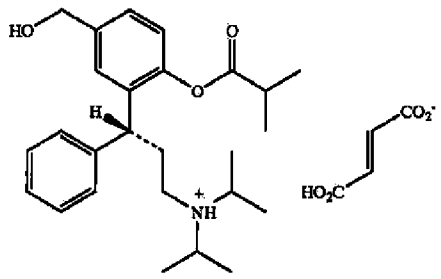
Melting point 102.3° C.
DC (1): 0.57
$[I]_D^{20}$=+21.3 (c=1.0, ethanol).
^{13}C-NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

5. Preparation of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenolisobutyrate ester (1)



A solution of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) and triethylamine (20.4 g, 201.7 mmol) in 750 ml dichloromethane has a solution of isobutyrate chloride (23.4 g, 201.7 mmol) in 250 ml dichloromethane added under agitation and cooling. Following addition agitation takes place for a further 15 minutes at 0° C., then for 30 minutes at room temperature and then one after another washing with water (250 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic phase is separated and concentrated on the rotary evaporator until dry. The ester R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is obtained as a colourless, viscous oil; yield: 77.1 g (98.4% of theoretical).
DC (1): 0.26; $[I]_D^{22}$=+2.7 (c=1.0, ethanol).
^{13}C-NMR ($CDCl_3$): 19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125:59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Preparation of R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.



A solution of 41.87 g (102 mmol) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester in 90 ml 2-butanone has fumaric acid (11.81 g, 102 mmol) added while heating. Following dissolution of the acid, cyclohexane (20–30 ml) is slowly added under agitation until the onset of turbidity. The colourless, homogenous deposit is initially left for 18 hours at room temperature, and then for several hours at 0° C. The colourless crystals that have precipitated are sucked off, washed with a little cyclohexane/2-butanone (90:10, vol.-%)and dried in the vacuum at 30° C. 44.6 g (83.1% of theoretical) hydrogen furate salt of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-

hydroxymethylphenyl-isobutyrate ester in the form of colourless flakes are obtained.

Melting point 98.8° C., a second crystallisation from the same solvent mixture provides a product with a melting point of 103° C.

$[I]_D^{20=+6.0}$ (c=1.0, ethanol).

Elementary analysis: Calculated for $C_{30}H_{41}NO_7$ (molecular weight 527.66) C 68.29%, H 7.83%, N 2.65%, O 21.2%; found C, 68.29%; H, 7.90%; N, 2.72%; O, 21.0%.

UV/VIS at Σ in nm ($A^{1\%}_{1\ cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

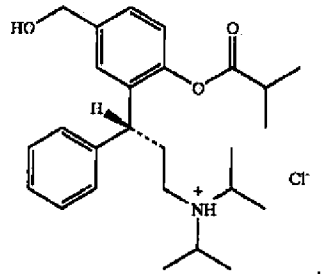
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 (CH_2OH); 6.832 (=CH, fumarate); 6.84–7.62 (aryl, =CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CHCH_2$); 34.09 (CH—C=O); 41.87 ($CHCH_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, fumarate); 170.48 (C=O, fumarate); 175.62 (i-Pr—C=O).

Ms in the direct inlet, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Preparation of R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrochloride hydrate



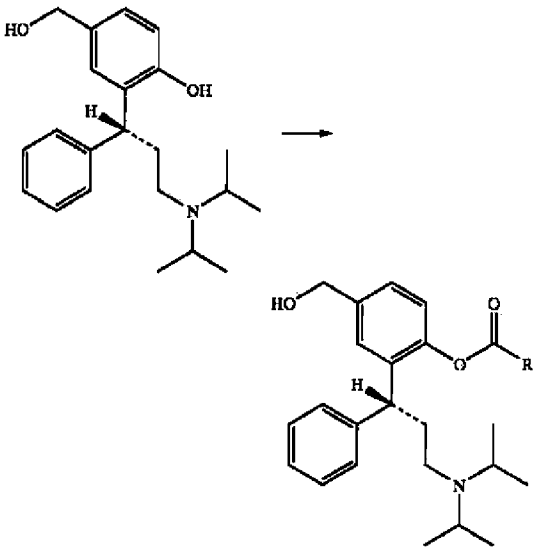
A solution of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester (8.54 g, 25.0 mmol) in 50 ml dichloromethane is slowly dropped at 0° C. into an agitated solution of isobutyrate chloride (2.66 g, 25.0 mmol) in 100 ml dichloromethane. After an hour the cooling is removed and re-agitation takes place for an additional hour. Following the drawing off of the volatile components in the vacuum on the rotary evaporator a colourless, amorphous-solid foam remains. This residue is dissolved in acetone (17 ml), with 0.45 to 0.50 g water and diethyl ether is added (approx. 20–25 ml) until there is a definite onset of turbidity. Following brief treatment with ultrasound crystallisation starts spontaneously and under agitation a further 80 ml of diethyl ether are slowly added. The precipitated colourless crystals are sucked off and dried overnight in the vacuum via phosphorous pentoxide. 10.5 g (93.7% of theoretical) colourless crystalline R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate with a purity of 97.0% (HPLC) are obtained.

Melting point 97.1° C.

$[I]_D^{20=+}$4.3 (c=1.03, ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolic Monoester



General Work Specification for the Manufacture of Phenolic Monoesters

Into a solution of 120.3 mg (0.352 mmol)R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml dichloromethane, under agitation at 0° C., a solution of acid chloride (0.352 mmol) in 2 ml dichloromethane is dropped. Then triethylamine-dichloromethane (49.1 µl/0.353 mmol-2 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with 5 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R=$CH_2CH(CH_3)_2$

R-(+)-3-methylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester

Colourless oil with 70% yield and >95% purity (NMR).

^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.

DC (1): 0.76.

R=$CH_2C(CH_3)_3$

R-(+)-3.3-dimethylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base

Colourless oil with 69.7% yield and >95% purity (NMR).

^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.

DC (1): 0.75.

R=$(CH_3)_3C$

R-(+)-3-pivalic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride.

Colourless crystals, melting point 165–6° C.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R=c-C_3H_5

R-(+)-cyclopropane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride.

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35, 129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R=c-C_4H_7

R-(+)-cyclobutane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R=c-C_5H_9

R-(+)-cyclopentane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R=c-C_6H_{11}

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6=39.7 ppm): 174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R=4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-ethylcarbonyloxy-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 195–8° C.

^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H can be substituted with D_2O, NH), 8.19–8.12 (m, 2H, Phenyl-H), 7.55 (d, J=1.0 Hz, 1H, Phenyl-H3), 7.41–7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J=7.6 Hz, 1H, CH), 3.61–3.50 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.97–2.74 (m, 2H, CH_2), 2.67 (q, J=7.4 Hz, 2H, CH_2), 2.56–2.43 (m, 2H, CH_2), 1.23–1.13 (m, 15H, 2×CH($C\underline{H}_3)_2$, CH_3).

R=4-(i-$C_3H_7CO_2$)—C_6H_4

R-(+)-4-(isopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 202–4° C.

^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H can be substituted with D_2O, NH), 8.19–8.12 (m, 2H, Phenyl-H), 7.55 (d, J=1.4 Hz, 1H, Phenyl-H), 7.42–7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.61–3.50 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.99–2.78 (m, 3H, CH_2, C<u>H</u>$(CH_3)_2$), 2.54–2.47 (m, 2H, CH_2), 1.29–1.13 (m, 18H, 3×CH($C\underline{H}_3)_2$)

R=4-(t-$C_4H_9CO_2$)—C_6H_4

R-(+)-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base.

Colourless oil.

^{1}H-NMR (DMSO-d_6): 8.19–8.12 (m, 2H, phenyl-H), 7.45–7.33 (m, 3H, phenyl-H), 7.25–7.09 (m, 7H, phenyl-H), 5.20 (t, J=5.6 Hz, 1H, OH), 4.50 (d, J=5.6 Hz, 2H, CH_2), 4.20 (t, J=7.5 Hz, 1H, CH), 2.95–2.80 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 2.38–2.25 (m, 2H, CH_2), 2.09–2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82–0.76 (m, 12H, 2×CH(C<u>H</u>$_3)_2$).

Hydrochloride: colourless crystals, melting point 165–6° C.

^{1}H-NMR ($CDCl_3$): 8.22–8.16 (m, 2H, phenyl-H), 8.02 (d, J=1.8 Hz, 1H, phenyl-H), 7.27–7.02 (m, 9H, phenyl-H), 4.83–4.60 ('m', 2H, CH_2), 4.01–3.94 (m, 1H, CH), 3.66–3.54 (m, 2H), 3.18–2.80 (m, 3H), 2.53–2.44 (m, 1H) (2×CH_2, 2×C<u>H</u>$(CH_3)_2$), 1.43–1.25 (m, 21H, $(CH_3)_3$, 2×CH($C\underline{H}_3)_2$).

R=4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(cyclopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 208–213° C.

^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H can be substituted with D_2O, NH), 8.15–8.09 (m, 2H, phenyl-H), 7.53 ('d', 1H, phenyl-H3), 7.42–7.13 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.62–3.53 (m, 2H, 2×C<u>H</u>(CH3)2), 3.05–2.70 (m, 2H, CH2), 2.51–2.37 (m, 2H, CH2), 2.01–1.89 (m, 1H, cyclopropyl-CH), 1.20–1.05 (m, 16H, 2×CH($C\underline{H}$3)2, 2×cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6=39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R=4-(c-$C_4H_7CO_2$)-C_6H_4

R-(+)-4-(cyclobutylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 201–6° C.

^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H can be substituted with D_2O, NH), 8.17–8.12 (m, 2H, phenyl-H), 7.54 (d, J=1.4 Hz, 1H, phenyl-H3), 7.42–7.14 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J=7.5 Hz, 1H, CH), 3.62–3.47 (m, 3H, cyclobutyl-CH), 2×C<u>H</u>$(CH_3)_2$), 3.00–2.70 (m, 2H, CH_2), 2.51–2.26 (m, 6H, CH_2, 2×cyclobutyl-CH_2), 2.10–1.85 (m, 2H, cyclobutyl-CH_2), 1.22–1.12 (m, 12H, 2×CH($C\underline{H}_3)_2$).

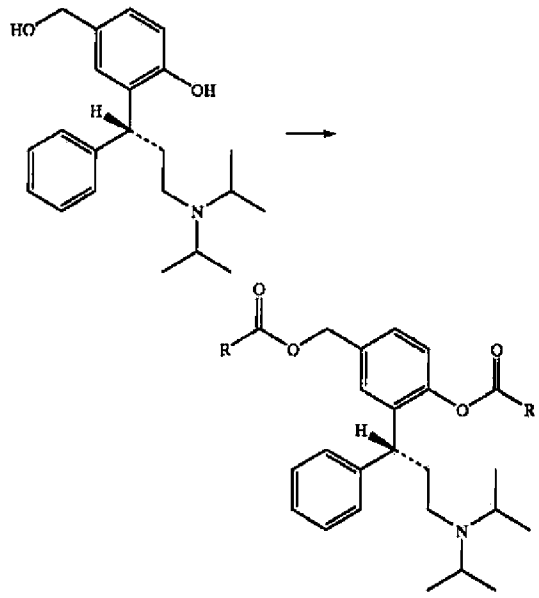
R=4-(c-$C_6H_{11}CO_2$)-C_6H_4

R-(+)-4-(cyclohexylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 212–217° C.

^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, can be substituted with D_2O, NH), 8.16–8.12 (m, 2H, phenyl-H), 7.54 (d, J=1.4 Hz, 1H, phenyl-H3), 7.39–7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, can be substituted with D_2O), 4.53 (d, J=4.2 Hz, 2H, CH_2), 4.22 (t, J=7.5 Hz, 1H, CH), 3.62–3.48 (m, 2H, 2×C<u>H</u>$(CH_3)_2$), 3.00–2.60 (m, 3H, cyclohexyl-CH), CH_2), 2.51–2.40 (m, 2H, CH_2), 2.07–1.98 (m, 2H, cyclohexyl-CH_2), 1.80–1.11 (m, 20H, 4×cyclohexyl-CH_2), 2×CH(C<u>H</u>$_3)_2$)

9. Identical Diesters



General Work Specification for the Manufacture of Identical Diesters

Into a solution of 7.30 g (21.4 mmol)R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml dichloromethane, under agitation at 0° C., a solution of acid chloride (49.2 mmol) in 50 ml dichloromethane is dropped. Then triethylamine-dichloromethane (6.86 ml/49.2 mmol-50 ml) is added. After 1–3 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 100 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via, sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R=Methyl

R-(−)-acetic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, free base

Pale yellow oil, purity (HPLC): 95.2%.

^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.

LC-MS: 425 (15%, M^+), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).

$[\alpha]_D^{20}$=−33.1 (c=1, CH_3CN).

DC (1): 0.79.

R=Cyclohexyl

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Pale yellow oil, purity (NMR): >95%.

^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.

DC (1): 0.96.

R=Isopropyl

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Free base: pale yellow oil, purity (HPLC): 95.6%.

^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.

DC (1): 0.74.

Hydrogen fumarate salt: colourless syrup, 94.4% HPLC purity.

^{13}C-NMR ($CDCl_3$): 17.89, 18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

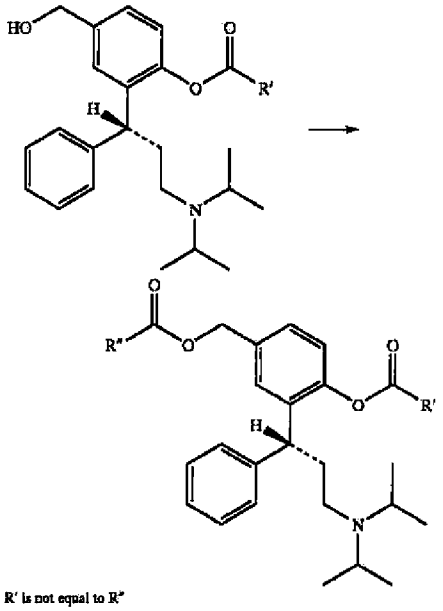
R=4-(t-C_4H_9 CO_2)-C_6H_4

R-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoic acid)-phenyl-ester hydrochloride

Colourless crystals, melting point 105–7° C.

^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Mixed Diesters



R' is not equal to R"

General Work Specification for the Manufacture of Mixed Diesters

Into a solution of 5.30 mmol phenolic monoester of general formula A in 40 ml dichloromethane under agitation at 0° C. a solution of acid chloride (5.83 mmol) in 15 ml dichloromethane is dropped. Then triethylamine-dichloromethane (0.589 g/5.82 mmol-15 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 50 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following example is manufactured using this method:

R'=$CH(CH_3)_2$

R"=CH_3

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Colourless oil.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

Hydrochloride: colourless crystals

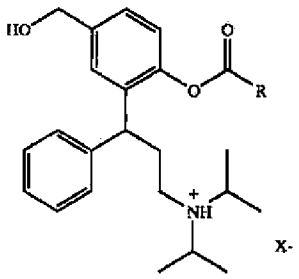
^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$=14.6 (c=1, $CHCl_3$).

What is claimed is:

1. Compounds of general formula I

Formula I

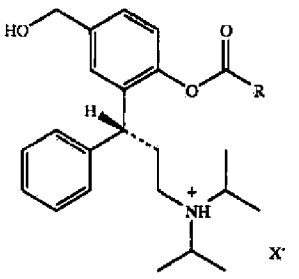


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

2. Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+) -tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

3. Compounds in accordance with claims 1, characterised in that they have general formula 2:

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

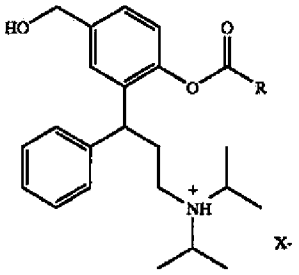
4. Compounds in accordance with claim 3, characterised in that X in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid, phthalic acid, methanesulfonic acid or orotic acid.

5. Compounds in accordance with claims 3, characterised in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl -phenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

6. Compounds in accordance with claims 3, characterised in that R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

7. Method for manufacturing compounds of general formula I

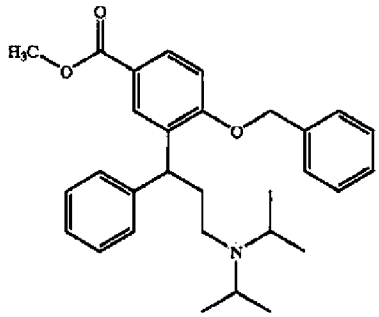
Formula I



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X– is the acid residue of a physicologically compatible inorganic or organic acid, characterised in that

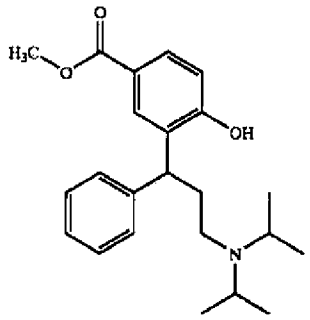
a) a compound of formula III

Formula III



is split with a hydrogenation agent to form a compound of Formula V

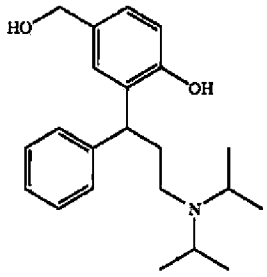
Formula V



whereupon

b) the compoud of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI

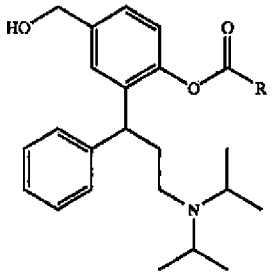
Formula VI



which

c) is converted with an acylation agent, in order to obtain a compound of formula A

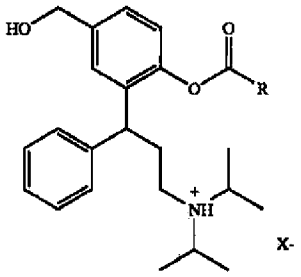
Formula A



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

Formula I

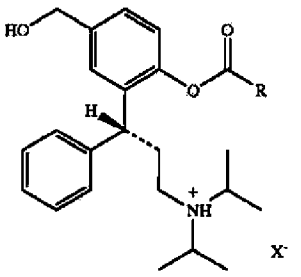


in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

8. Method in accordance with claim 7, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

9. Method for manufacturing compounds of general formula 2

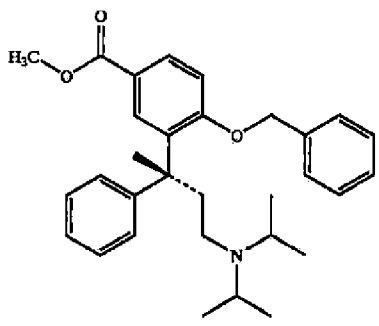
Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

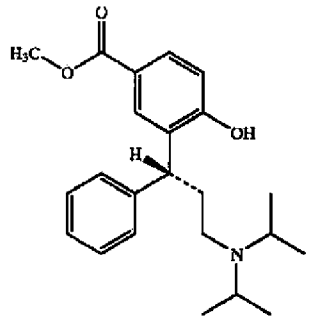
a) a compound of the formula 3

Formula 3



s split with a hydrogenation agent to form a compound of formula 5

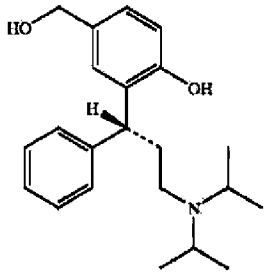
Formula 5



whereupon

b) the compound formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6

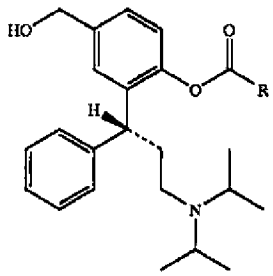
Formula 6



which

c) is converted with an acylation agent, in order to obtain a compound of formula 1

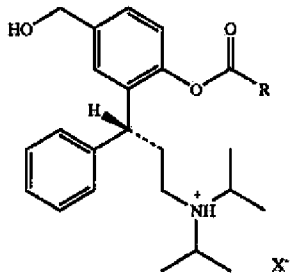
Formula 1



in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X– is the acid residue of a physiologically compatible inorganic or organic acid.

10. Method in accordance with claim **9**, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(−)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(−)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

11. Method in accordance with claims **7**, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

12. Method in accordance with claims **7**, characterised in that for the reducing agent $NaBH_4EtOH$, preferably $LiAlH_4$/THF, is used.

13. Method in accordance with claims **7**, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

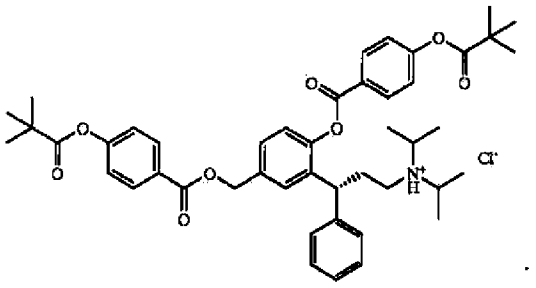
14. Method in accordance with claims **9**, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate.

15. Method in accordance with claims **9**, characterised in that R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid or hydrochloric acid are converted with the formation of the respective salt.

16. Method in accordance with claims **9** for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of isobutyryl chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

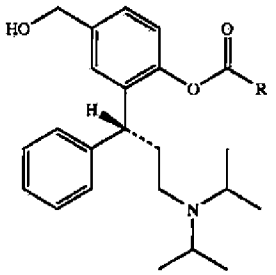
17. Compound of formula 7

Formula 7



18. A method of manufacture of phenolic monoesters of general formula 1

Formula 1



wherein the method comprises the steps of:

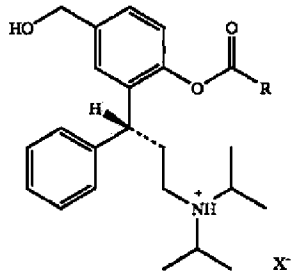
providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

19. A method of manufacture of salts of phenolic monoesters of general formula 2:

Formula 2



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physicologically compatible inorganic or organic acid, wherein the method comprises the steps of:

providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

20. A method of manufacture of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate or R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate, the method comprising the steps of;

providing a compound of claim 17;

deprotecting the hydroxyl residues of the 4-hydroxybenzyl alcohol residue; and

acylating the phenol residue.

21. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.

22. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.

23. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.

24. The method of any one of claims 21–23, wherein the urinary incontinence disorder is urge incontinence.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 17, please correct "prodrugn" to -- prodrugs --
Line 26, please correct "3,3-diphenylpropylarines" to -- 3,3-diphenylpropylamines --

Column 3,
Line 50, please correct "and X" to -- and X^- --

Column 4,
Lines 45-46, please correct "are that" to -- are manufactured in that --

Column 5,
Line 24, please correct "with agent" to -- with a reducing agent --

Column 13,
Line 14, please correct "photometer. model" to -- photometer model --
Line 64, please correct "43.63" to -- 43.83 --

Column 15,
Line 37, please correct "amorphous. solid" to -- amorphous solid --

Column 16,
Line 37, please correct "125:59" to -- 125.59 --

Column 17,
Line 6, please correct "$[I]_D^{20=+6.0}$" to -- $[I]_D^{20}$= +6.0 --
Line 23, please correct "Ms" to -- MS --

Column 23,
Line 13, please correct "=14.6" to -- = +14.6 --
Line 47, "please correct "claims" to -- claim --

Column 24,
Lines 15 and 21, please correct "claims" to -- claim --
Line 46, please correct "physicologically" to -- physiologically --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,858,650 B1
DATED : February 22, 2005
INVENTOR(S) : Meese

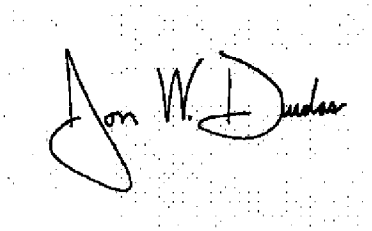
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,
Lines 35, 38, 41, 45, 53 and 58, please correct "claims" to -- claim --

Column 30,
Line 17, please correct "physicologically" to -- physiologically --

Signed and Sealed this

Ninth Day of August, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT H

US007230030B2

(12) **United States Patent**
Meese et al.

(10) **Patent No.: US 7,230,030 B2**
(45) **Date of Patent: Jun. 12, 2007**

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

(75) Inventors: **Claus Meese**, Monheim (DE); **Bengt Sparf**, Trangsund (SE)

(73) Assignee: **Schwarz Pharma AG**, Monheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 94 days.

(21) Appl. No.: **10/766,263**

(22) Filed: **Jan. 27, 2004**

(65) **Prior Publication Data**

US 2004/0186061 A1 Sep. 23, 2004

Related U.S. Application Data

(63) Continuation of application No. 09/700,094, filed as application No. PCT/EP99/03212 on May 11, 1999, now Pat. No. 6,713,464.

(30) **Foreign Application Priority Data**

May 12, 1998 (EP) 98108608

(51) **Int. Cl.**

A01N 37/02	(2006.01)
A01N 37/06	(2006.01)
A61K 31/225	(2006.01)
C07C 69/34	(2006.01)
C07C 211/00	(2006.01)

(52) **U.S. Cl.** **514/548**; 514/648; 560/194; 564/316

(58) **Field of Classification Search** 560/194; 564/316; 514/548, 648

See application file for complete search history.

(56) **References Cited**

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(Continued)

Primary Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon LLP

(57) **ABSTRACT**

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 relates to novel prodrugs of anti-muscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, 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.

14 Claims, 1 Drawing Sheet

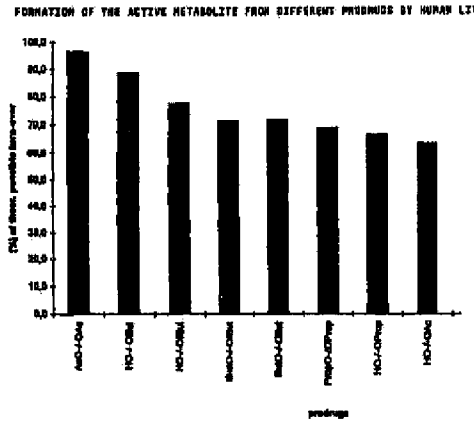

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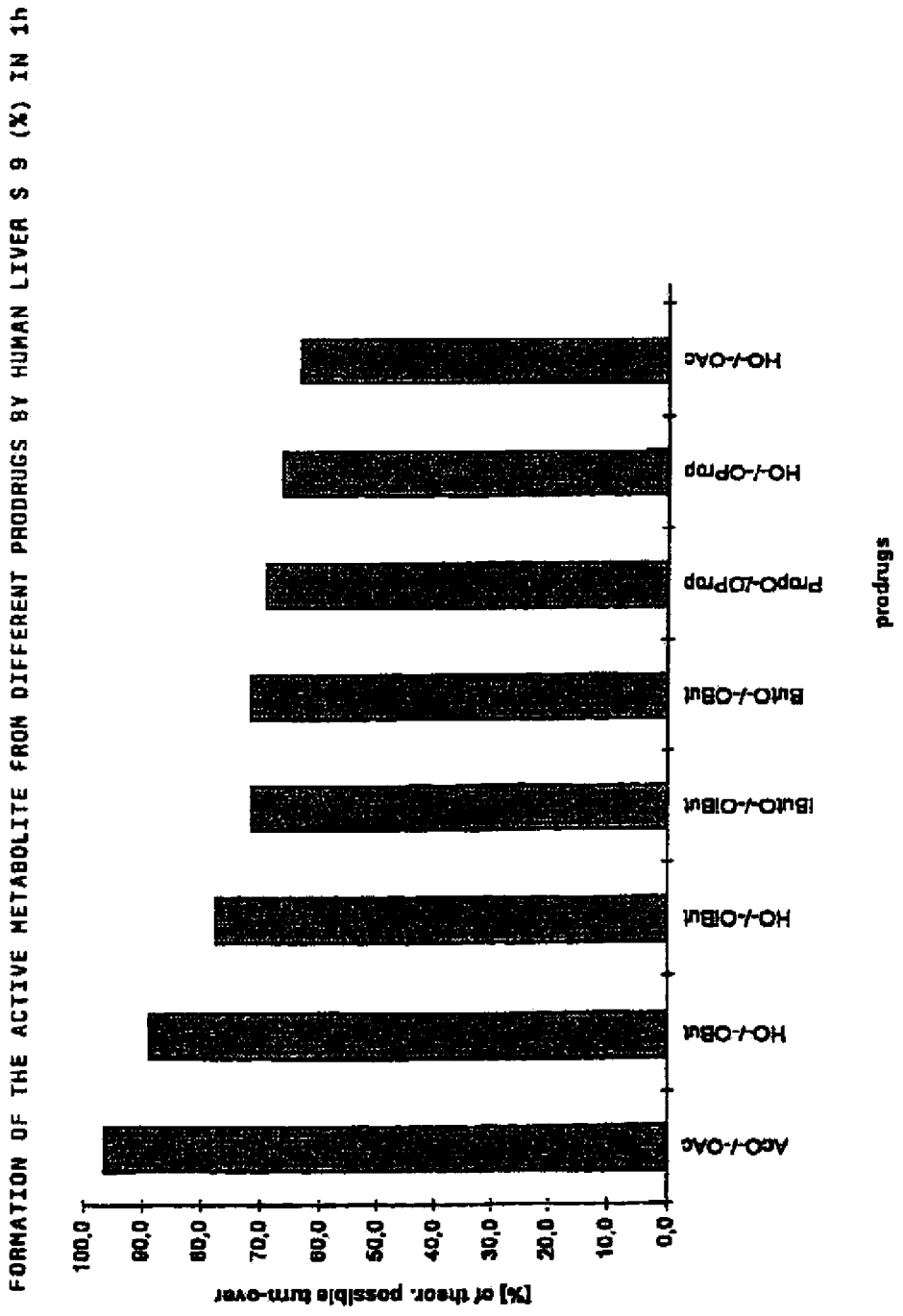
FIG. 1


FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
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80,0
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60,0
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30,0
20,0
10,0
0,0
ACO-/-OAc
HO-/-OBut
HO-/-OIBut
IBuO-/-OIBut
BuO-/-OBut
PrpO-/OPrp
HO-/-OPrp
HO-/-OAc
prodrugs

DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The present application is a Continuation Application of U.S. Ser. No. 09/700,094, filed Jan. 2, 2001, now U.S. Pat. No. 6,713,464, which in turn claimed the priority benefit of PCT/EP99/03212, filed May 11, 1999.

BACKGROUND OF THE INVENTION

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.

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.

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).

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.

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.

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.

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.

SUMMARY OF THE INVENTION

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.

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.

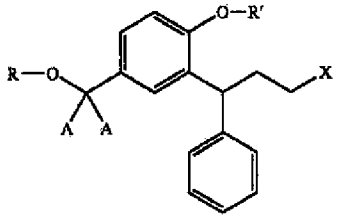
BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows the formation of the active metabolite from different prodrugs by human liver S 9(%) in 1 hour.

DETAILED DESCRIPTION OF THE INVENTION

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

Formula I



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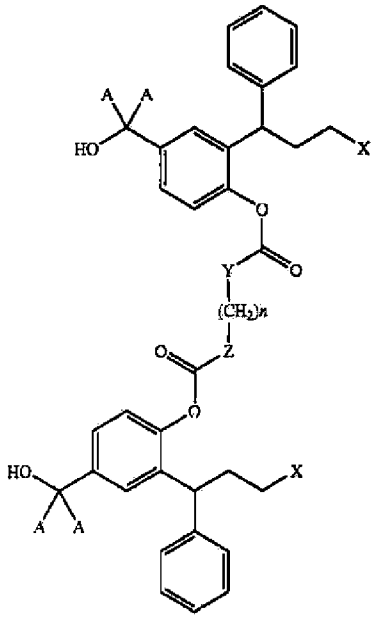
Formula VII'



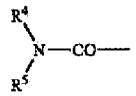
wherein R and R' are independently selected from

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

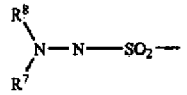
c) C_1–C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

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,

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.

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, hydrobromide and the like.

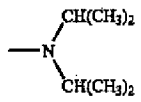
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

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.

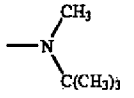
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

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

a)



b)



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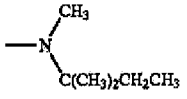

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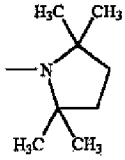

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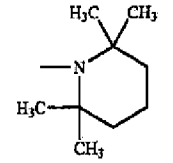
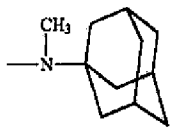


e)



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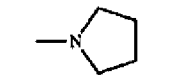
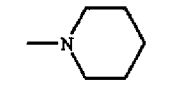


g)



h)

Group a) is particularly preferred.

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.

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.

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, nitro and the like. 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.

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.

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

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

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.

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.

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.

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

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 correponding 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.

The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

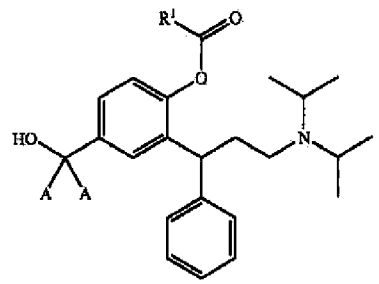
The term "Bn" as used herein denotes a benzyl group.

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

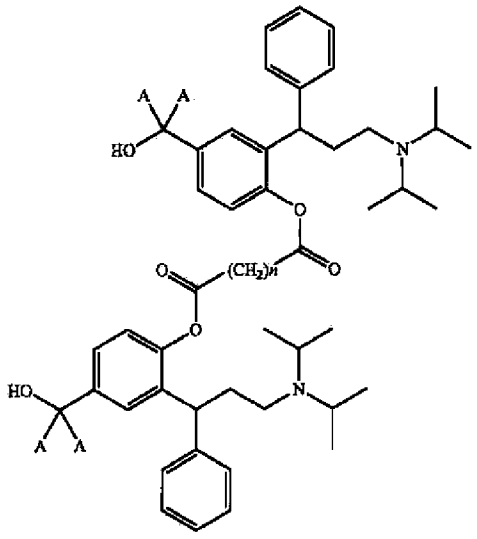
Preferred compounds according to the present invention are:

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-diisopropylamino-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,

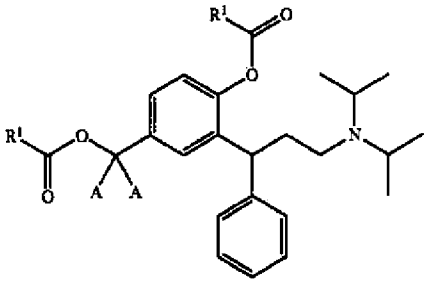
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-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,

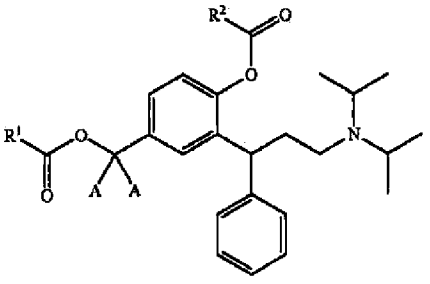
cyclic oct-4-ene-1,8-dioate of Intermediate B,

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,

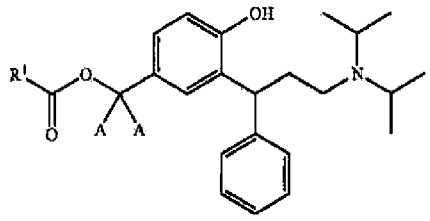
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-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



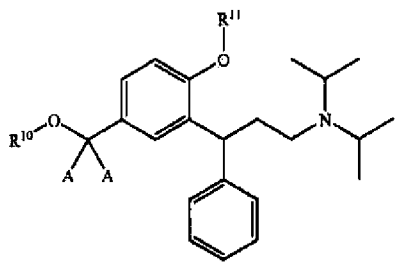
wherein R^1 is as defined above.

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



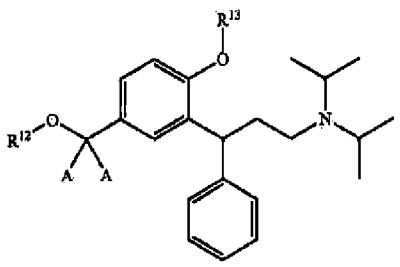
wherein at least one of R^{10} and R^{11} is selected from C_1–C_6 alkyl, benzyl or $—SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1–C_6 alkylcarbonyl or benzoyl.

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-diphenylsilanyloxy-methyl)-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



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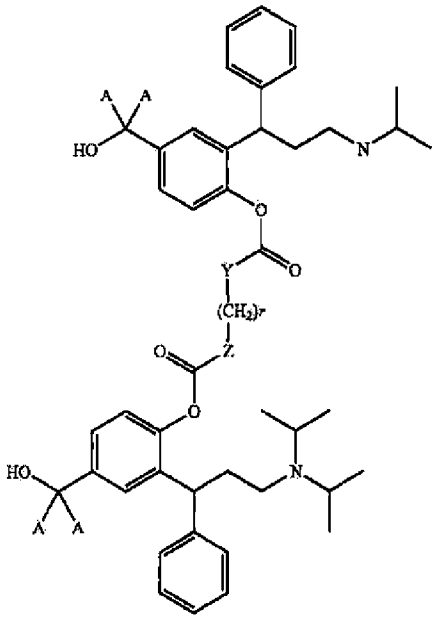
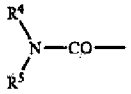
Formula VIII



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 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,

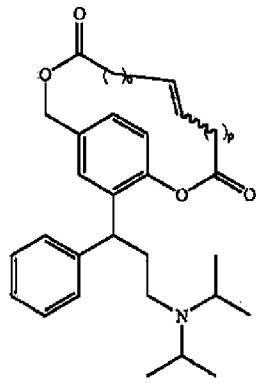
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

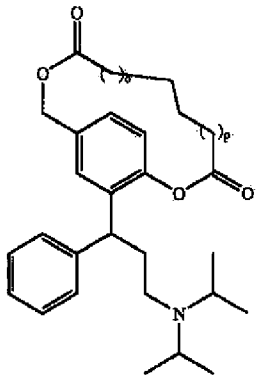
G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'

Formula IX



Formula IX'

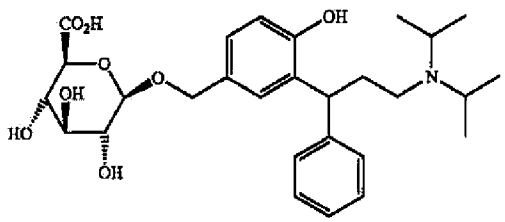


wherein o and p are the same or different and represent the number of methylene units $-(CH_2)-$ and may range from 0 to 6,

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

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

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



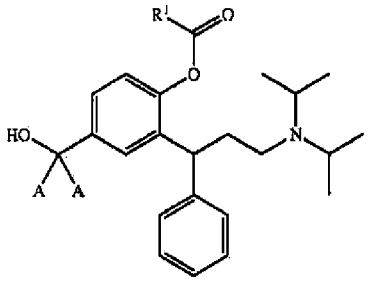
and

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.

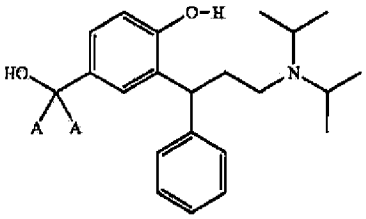
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

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

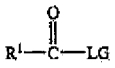
Formula II



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

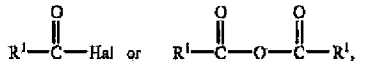


with an equivalent of an acylating agent selected from



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.

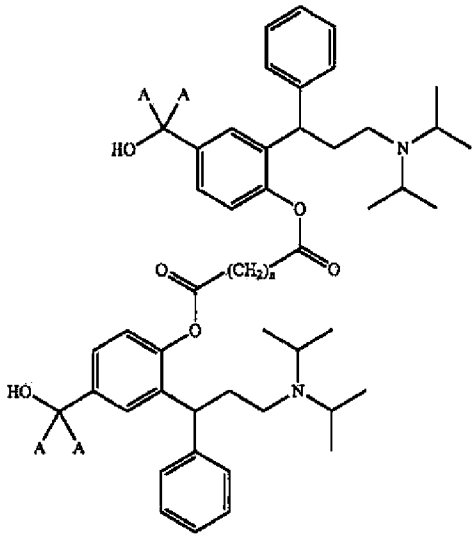
Preferably, the acylating agent is selected from



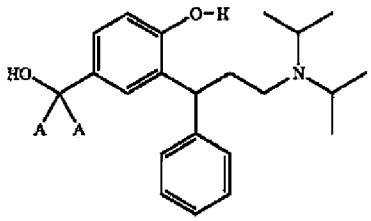
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

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

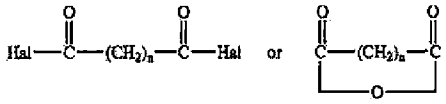
Formula II'



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

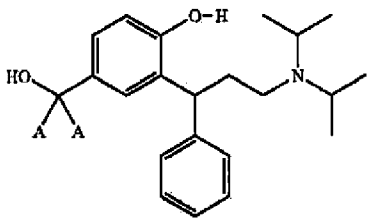


with an acylating agent selected from



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

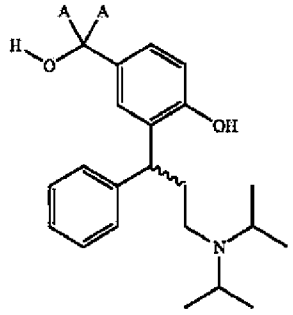
Hence, in these processes, an Intermediate B having the formula



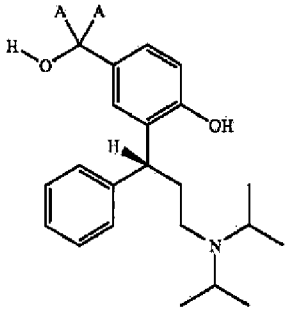
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n is 0–12), respectively, if polyfunctional acylating agents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

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:

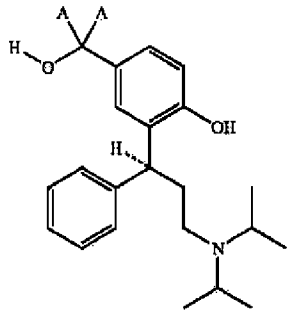
Intermediate RS



Intermediate R-(+)



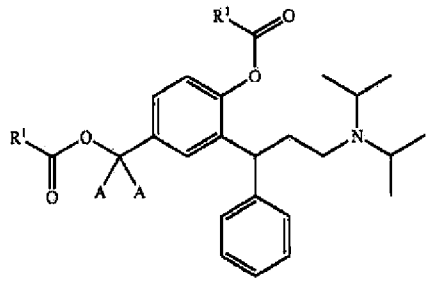
Intermediate S-(-)



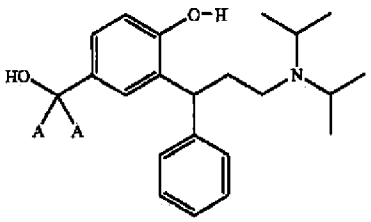
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III

Formula III

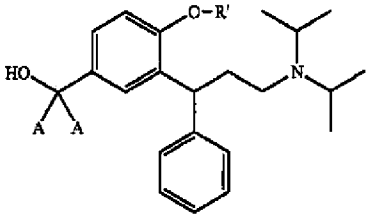


as defined above can be prepared by a process which comprises treatment of a compound of the formula



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

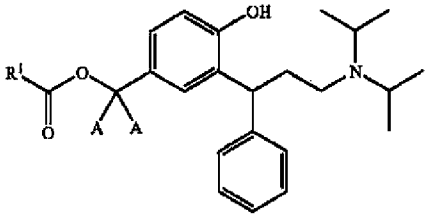
Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In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



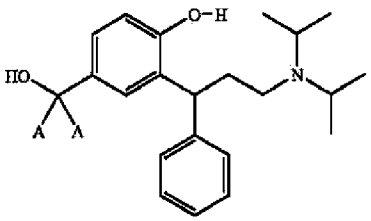
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes 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



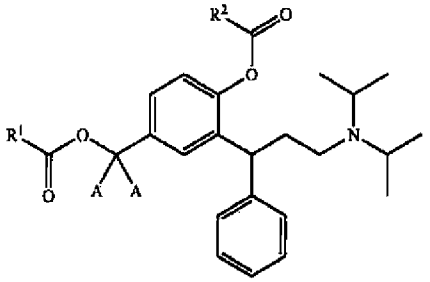
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

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 hydro-

gen 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.

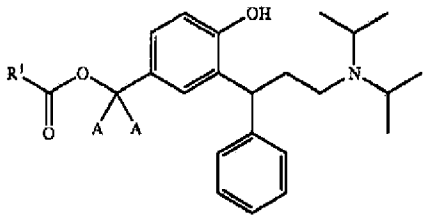
The mixed diesters represented by the general formula IV

Formula IV



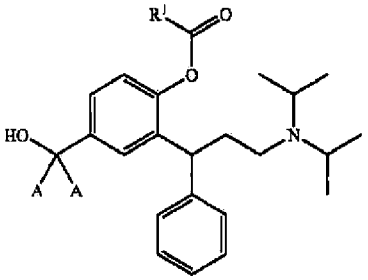
wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V

Formula V



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

Formula II

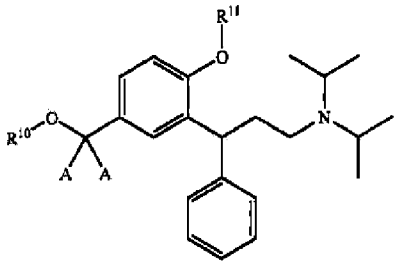


as defined hereinbefore.

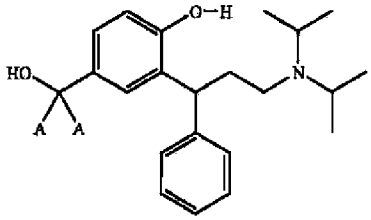
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI

Formula VI



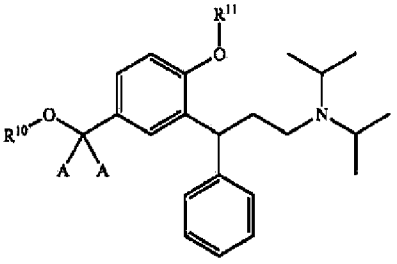
as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



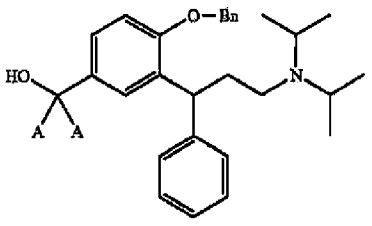
with an alcohol R^{10}—OH in the presence of an esterification catalyst.

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

Formula VI

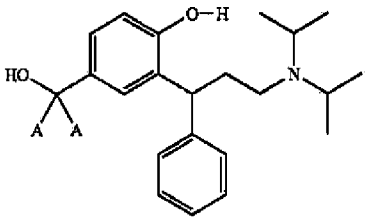


wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



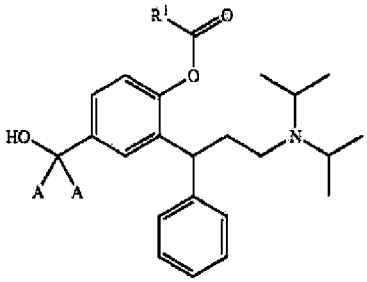
and

-continued



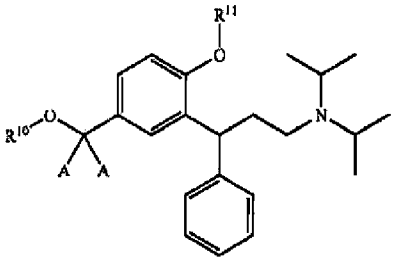
and

Formula II



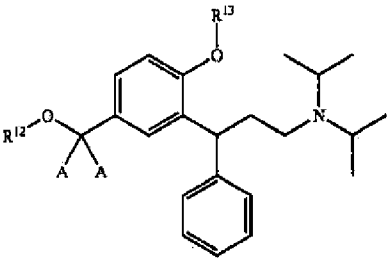
or

Formula VI

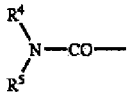


wherein R^{10} is hydrogen and R^{11} is as defined above or

Formula VII



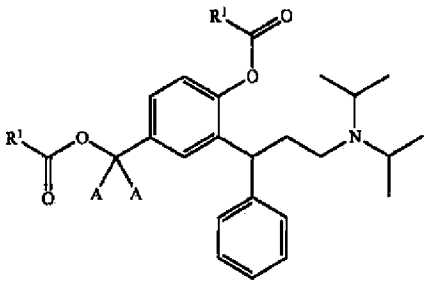
wherein R^{12} is hydrogen and R^{13} represents a C_1–C_6 alkoxycarbonyl group or



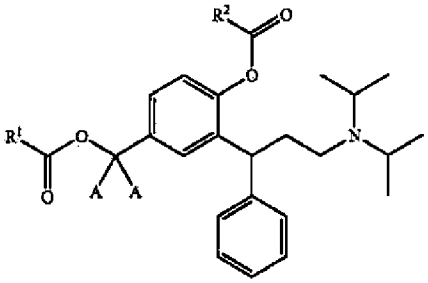
wherein R^4 and R^5 are as defined above

or of benzylic acylates selected from

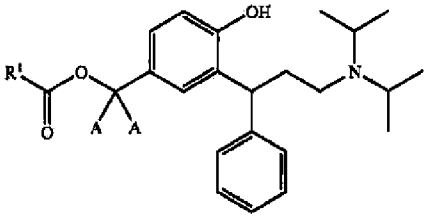
Formula III



Formula IV

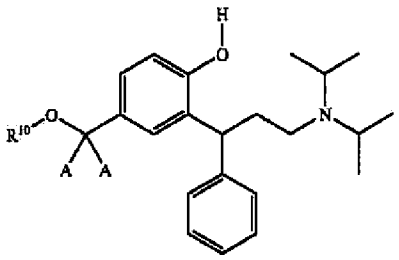


Formula V



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

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.

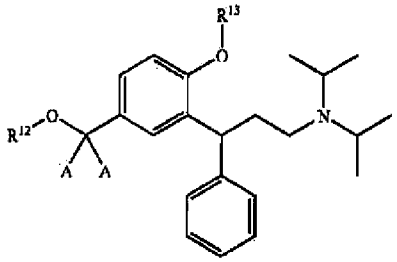
In summary, regioselective modification of the benzylic hydroxy groups is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J. M. Saa, 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]).

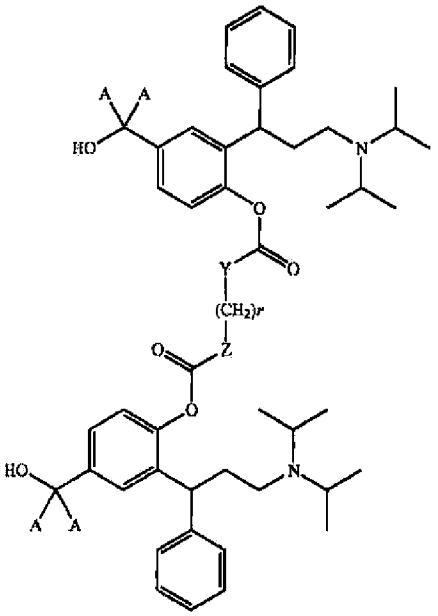
Likewise the phenolic hydroxy groups are readily transformed into phenyl ethers (R^{11}=alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis 1981, 1–28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate 3 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]).

Carbonates and carbamates represented by the general formulae VII and VIII

Formula VII

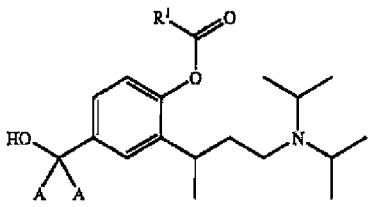


Formula VIII

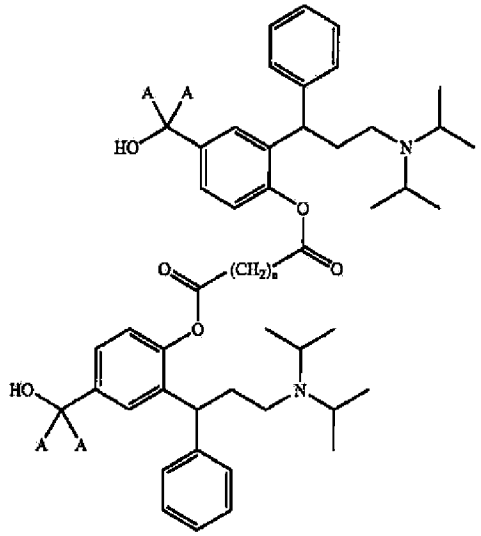


as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of

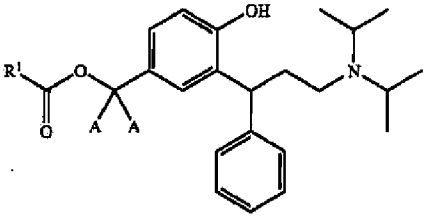
Formula II



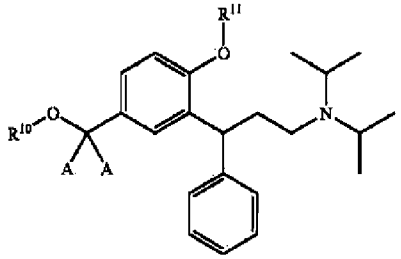
Formula II'



Formula V



Formula VI



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

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.

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.

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

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, for nasal spray administration or the like, in accordance with accepted pharmaceutical 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, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

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, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

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.

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.

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

I. EXPERIMENTAL

1. General

All compounds were fully characterized by ^{1}H 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. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5×10 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

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

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 ethylacetate. 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

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 (2×300 ml) and the extract was washed with water (2×200 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

A solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic 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%, $M^{+\cdot}$), 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%.

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

Warm solutions of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic 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.

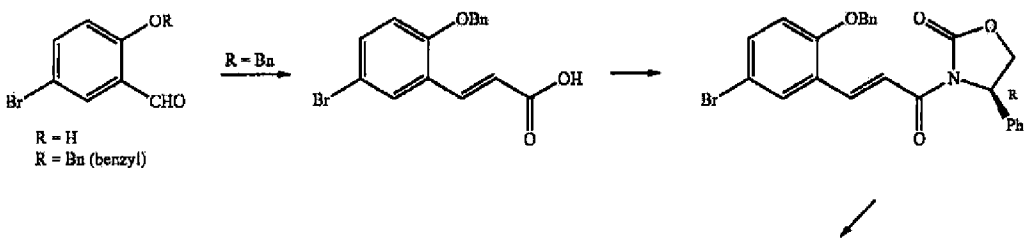
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichlotomethane (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

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 redissolved in dichloromethane (1.5 liter) 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.

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



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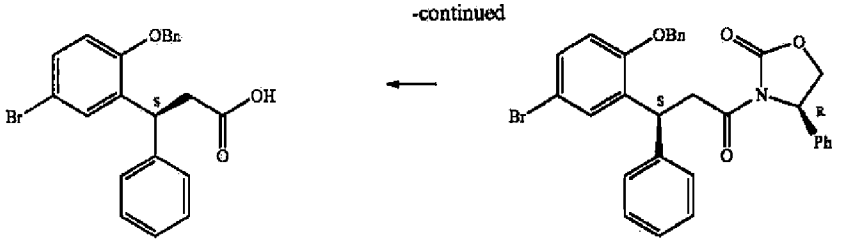


2-Benzyloxy-5-bromobenzaldehyde

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

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

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

To a precooled (−30° C.) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetraydrofuran (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

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.

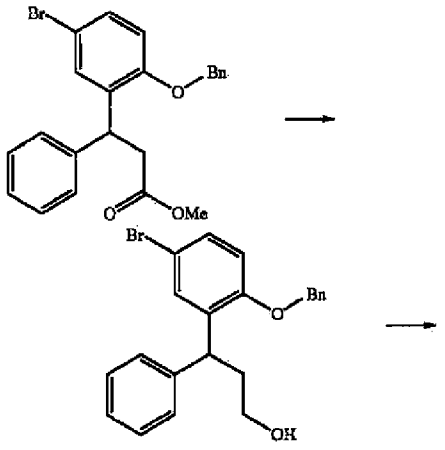
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by 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).

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

Conjugate organocuprate addition of phenylmagnesium-bromide 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-benzyloxy-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



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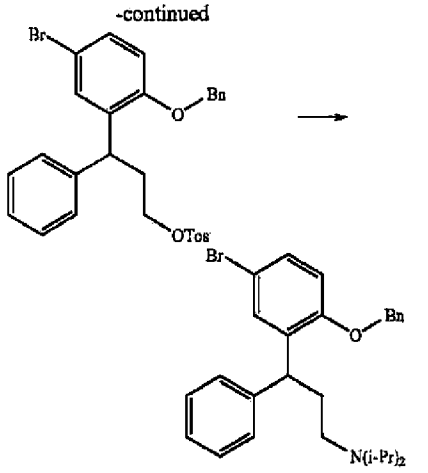


(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

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.

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.

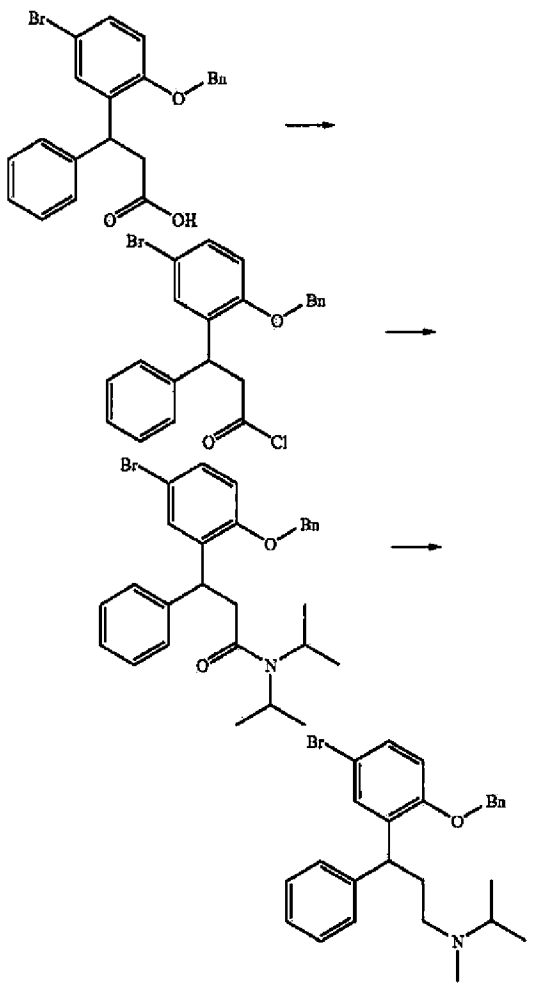
(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

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

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



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

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 g). 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

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

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

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/tetrahydrofuran (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

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

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%.

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

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

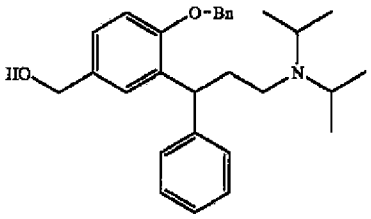
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to −60° C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and 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)

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 (2 h) 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-7-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)

Repetition of the above described reduction of the methyl ester 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.

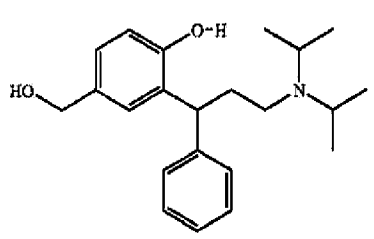
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Intermediate B (n=1)

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-diisopropylamino-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

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

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)

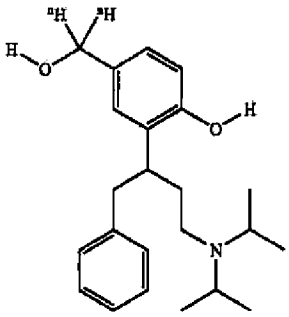
A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in 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, 144.80, 155.52.

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 (2×5 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

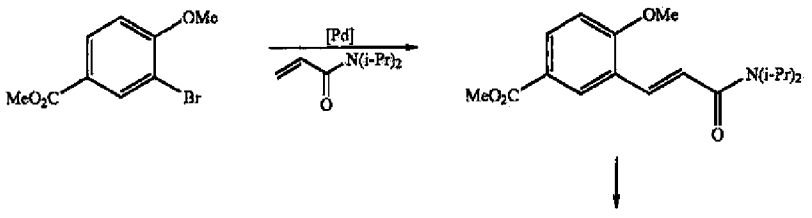


n=2, deuterium

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

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



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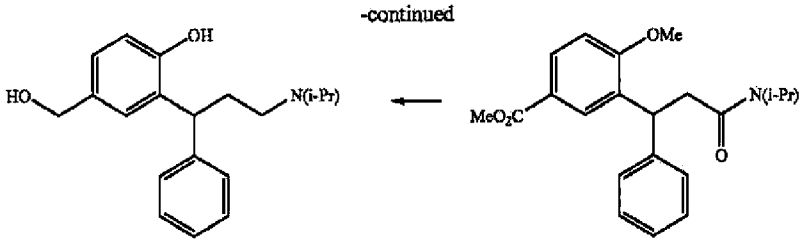


Intermediate B

N,N-Diisopropyl-acrylamide

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 (3×100 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)

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, 35.07. 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)

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^+, 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

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

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.

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).

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

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 purifies between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

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)

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).

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-7-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—Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (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, 164.99.

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, 4.66, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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 ($M^{+\cdot}$, 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, 42.3.9, 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

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that, 2.4 mmol of both triethylamine 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.

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-benzoyloxyznethyl-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

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.

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-7-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, 128.39, 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

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.

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

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.

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:

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.

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

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, 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, 129.42, 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%, $[M-HCl]^{+\cdot}$), 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.

(±)-22-(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-7-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

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

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.

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:

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.

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

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-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, 65.12, 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, 33.2.6, 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, 36.98, 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

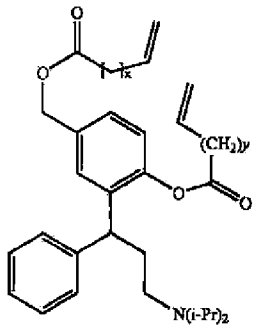
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-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)



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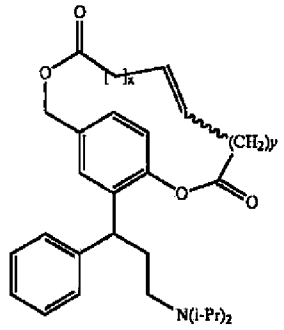
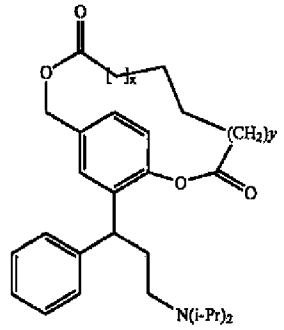




EXAMPLE

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

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-enoyloxymethyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 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, 1–36.38, 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-hydroxymethylphenol 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-diisopropylamino)-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.

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

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

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-hydroxymethylphenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 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 B 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

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

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

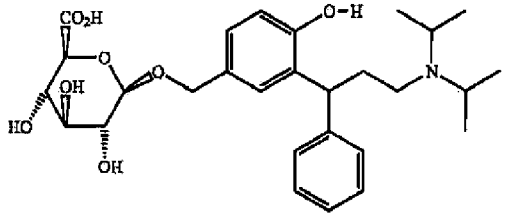
EXAMPLE

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethylphenyl ester Hydrochloride

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)



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 projection 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.

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

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.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, Mass., USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, Mass., 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.

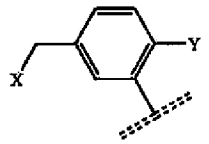
The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in FIG. 1.

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:

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

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.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

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%.

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

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

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.

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) contractile 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

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

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/cm²/24 hrs]
HO—/—OH	3
HO—/—OiBut	150
iButO—/—OiBut	60
PropO—/—OProp	70

Disubstitution 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.

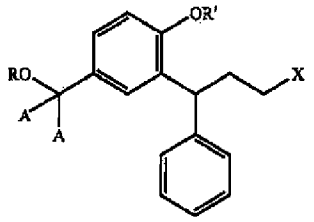
Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite,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

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

What is claimed is:

1. A 3,3-Diphenylpropylamine having the formula I:

Formula I



wherein R and R' are independently

hydrogen, C_1–C_6 alkyl, C_3–C_{10} cycloalkyl, substituted or unsubstituted benzyl, or allyl;

with the proviso that at least one of R' and R is not hydrogen, and the proviso that R' is not methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia

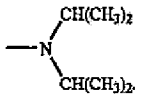
Formula Ia

wherein R^8 and R^9 represent C_1–C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

A represents hydrogen (^1H) or deuterium (^2H), and

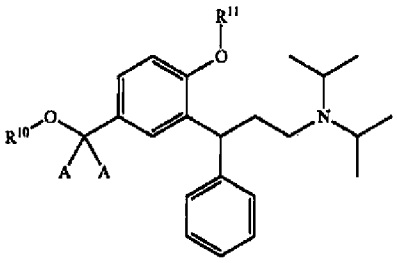
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. The 3,3-Diphenylpropylamine of claim 1, wherein X is



3. A 3,3-Diphenylpropylamine having the formula VI:

Formula VI



wherein A represents hydrogen (H) or deuterium (^2H), and

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

wherein one of R^{10} or R^{11} is selected from C_1–C_6 alkyl, allyl, or benzyl, and the other represents hydrogen,

with the proviso that R^{11} is not methyl or benzyl when R^{10} is hydrogen, and R^{10} is not ethyl when R^{11} is hydrogen.

4. The 3,3-Diphenylpropylamine of claim 3 selected from the group consisting of:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,

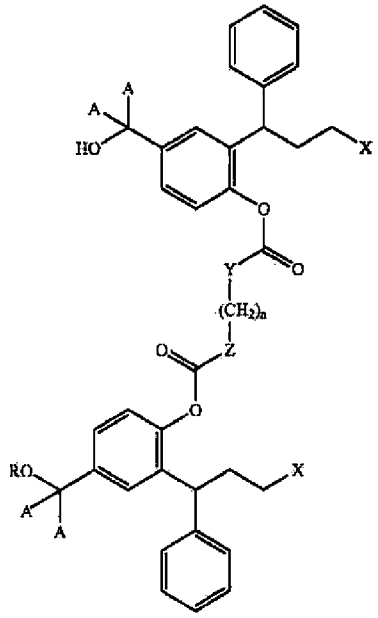
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol.

5. A 3,3-Diphenylpropylamine having the formula VII':

Formula VII'



wherein R is C_1–C_6 alkyl, C_3–C_{10} cycloalkyl, substituted or unsubstituted benzyl, or allyl;

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,

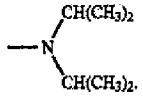
Y and Z independently represent O, S or NH,

A represents hydrogen (^{1}H) or deuterium (^{2}H),

n is 0 to 12, and

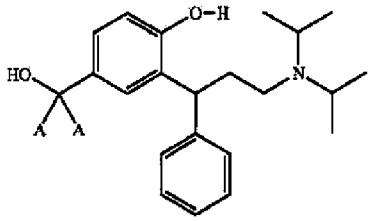
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

6. The 3,3-Diphenylpropylamines of claim 5, wherein X is



7. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1–6 and a pharmaceutically acceptable carrier.

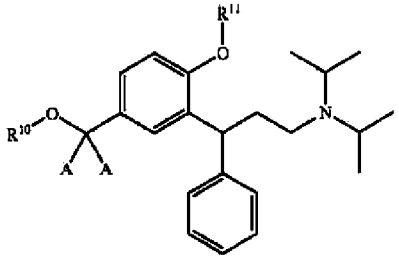
8. A process for the production of ethers according to claim 3, wherein R^{11} is hydrogen, which comprises reacting a compound of the formula



with an alcohol R^{10}—OH in the presence of a catalyst.

9. A process for the preparation of ethers of formula VI:

Formula VI



wherein A represents hydrogen (^{1}H) or deuterium (^{2}H), and

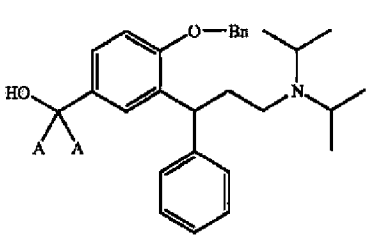
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers, and

wherein one of R^{10} or R^{11} is selected from C_1–C_6 alkyl, allyl, or benzyl, and the other represents hydrogen,

with the proviso that R^{11} is not methyl or benzyl when R^{10} is hydrogen, and R^{10} is not ethyl when R^{11} is hydrogen;

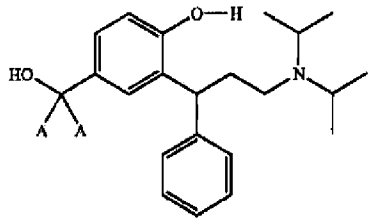
wherein the process comprises acid or base treatment, in the presence of at least one alcohol selected from R^{10}OH and R^{11}OH, of a compound selected from

(a)



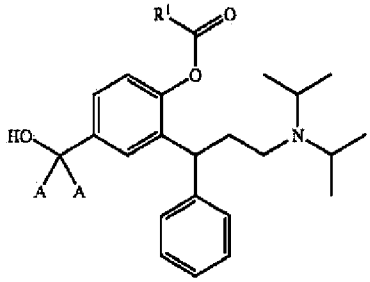
-continued

(b)



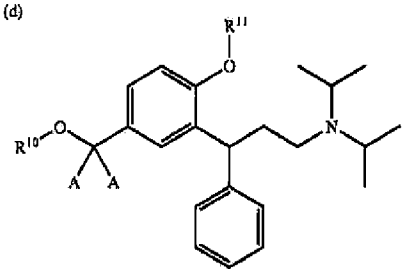
Formula II

(c)



Formula VI

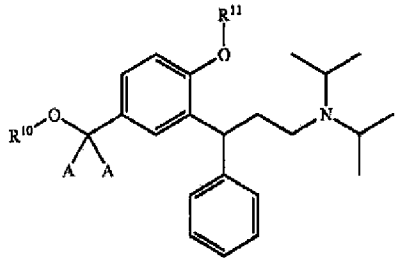
(d)



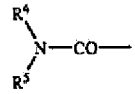
wherein R^{10} is hydrogen,

Formula VII

(e)



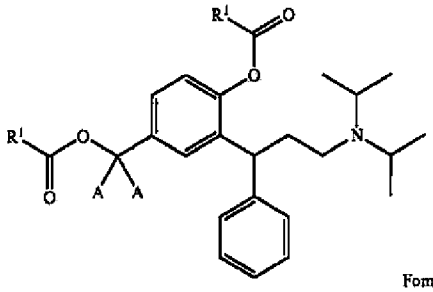
wherein R^{12} is hydrogen and R^{13} represents a C_1–C_6 alkoxycarbonyl group or



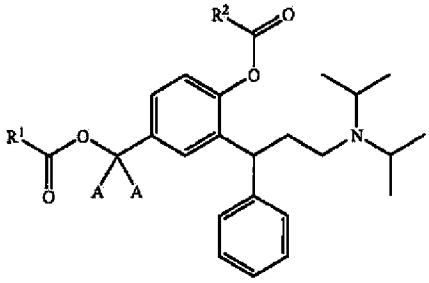
wherein R^4 and R^5 independently represent hydrogen, C_1–C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen, and

(f) benzylic acylates selected from

Formula III

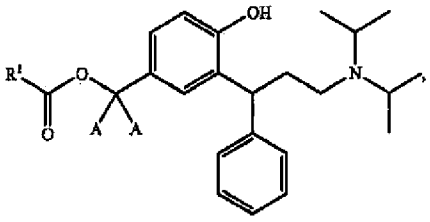


Formula IV



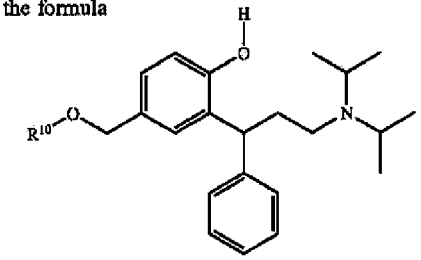
and

Formula V



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

10. A process for the preparation of ethers of formula VI according to claim **3**, which comprises treating a compound of the formula



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

11. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims **1**–**6**.

12. A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim **7** effective to diminish or eliminate symptoms of the disease.

13. The method according to claim **12** wherein the disease is urinary incontinence.

14. The method according to claim **13** wherein the mammal is a human.

* * * * *

Electronic Patent Application Fee Transmittal

Application Number:	11201756
Filing Date:	10-Aug-2005
Title of Invention:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
First Named Inventor/Applicant Name:	Claus Meese
Filer:	Willem deWeerd/Theresa Doonan
Attorney Docket Number:	12961/46103

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	2739649
Application Number:	11201756
International Application Number:	
Confirmation Number:	3812
Title of Invention:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
First Named Inventor/Applicant Name:	Claus Meese
Customer Number:	26646
Filer:	Willem deWeerd/Theresa Doonan
Filer Authorized By:	Willem deWeerd
Attorney Docket Number:	12961/46103
Receipt Date:	18-JAN-2008
Filing Date:	10-AUG-2005
Time Stamp:	16:24:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	2765
Deposit Account	110600
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	12961_46103_RCE_Dec_Exhibits.pdf	7573740 20ff12f1c6fa994391306bad685704031f380a253	no	180
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8178 113fd66c469051b725afbfa0fd94868a53a953d7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7581918		

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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/201,756	08/10/2005	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/18/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 20	= 2	X $ =		OR	X $50=	100
	Independent (37 CFR 1.16(h))	* 7	Minus	***4	= 3	X $ =		OR	X $210=	630
	☐ Application Size Fee (37 CFR 1.16(s))									
	☒ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		370
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	1100

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PAUL M. STANBACK/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 03/17/2008

PSTANBAC	SALE	#00000003	Mailroom Dt:	01/18/2008		110600	11201756
		01	FC : 1202	100.00	DA		
		02	FC : 1201	630.00	DA		
		03	FC : 1203	370.00	DA		

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/201,756	08/10/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☒ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							360
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	360

APPLICATION AS AMENDED – PART II

AMENDMENT	01/18/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 22	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 8	Minus	***7	= 1	X $ =		OR	X $210=	210
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	210

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/WILLIAM N. PHILLIPS/

Interview Summary	Application No.	Applicant(s)	
	11/201,756	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Zachary C. Tucker*. (3) *Steve Lee*.

(2) *Joe Coppolla*. (4)_____.

Date of Interview: *11 February 2008*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *none*.

Identification of prior art discussed: *none*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Zachary C. Tucker/
Primary Examiner, Art Unit 1624
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The issue of the disapproved Terminal Disclaimers was discussed,and applicants' coiunsel agreed to submit new Terminal Disclaimers signed by attorneys of record. Examiner Tucker asked if compounds covered in new claims 35-43 were claimed or covered by any copending applications or parent patents, and Mrs. Ccppolla and Lee indicated that they were covered by US 6,713,464, which will be one of the newly filed Terminal Disclaimers filed over the instant application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Meese et al.
SERIAL NO.	:	11/201,756
FILED	:	August 10, 2005
FOR	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
EXAMINER	:	Tucker
GROUP ART UNIT	:	1624

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 as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Date: February 19, 2008

Signature: /Theresa A.E. Doonan/
Theresa A.E. Doonan

TRANSMITTAL OF RESPONSE TO EXAMINER'S INTERVIEW SUMMARY

S I R:

In response to the Examiner's Interview of February 11, 2008, Applicant encloses herewith:

1. Examiner's Interview Summary:

2. Four (4) Terminal Disclaimers to Obviate a Double Patenting Rejection Over a Prior Patent/Application for the following patents: 6,858,650; 6,713,464 and the following patent applications: 10/533,683; 10/532,836;

3. A new copy of Exhibit A and Exhibit E, as filed January 18, 2008, as requested by the Examiner due to poor image quality.

No fees are believed due. In the event a determination is made that fees are due, the Commissioner is authorized to charge any such fees or credit any overpayment in connection with this paper to Deposit Account No. **11-0600.** A copy of this form is enclosed for charging purposes.

Respectfully submitted,

KENYON & KENYON LLP

Dated: February 19, 2008 By: /Joseph A. Coppola/
Joseph A. Coppola
(Registration No. 38,413)

One Broadway
New York, New York 10004
(212) 425-7200
CUSTOMER NO. 26646

Docket No.: 12961/46103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Meese et al.
SERIAL NO.	:	11/201,756
FILED	:	August 10, 2005
FOR	:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
EXAMINER:		Tucker
GROUP ART UNIT	:	1624

Mail Stop Amendment
COMMISSIONER FOR PATENTS
P.O. BOX 1450
Alexandria, VA 22313-1450

EXAMINER INTERVIEW SUMMARY

The Applicants thank the Examiner for the in-person interview extended to the Applicants' representatives Steven J. Lee and the undersigned on February 11, 2008. The interview included a discussion of the Terminal Disclaimers that were previously submitted in this application. The Applicants' representatives agreed to re-submit the Terminal Disclaimers under the signature of an attorney of record.

Accordingly, enclosed herewith are four Terminal Disclaimers. The four Terminal Disclaimers are the same as the Terminal Disclaimers previously submitted except that they are signed by the undersigned rather than by Dr. Dressen.

The pending claims were also discussed at the interview. In answer to the Examiner's question, the Applicants' representatives stated that the compounds recited in new claims 35-43 filed January 18, 2008 were within the scope of some of the claims of U.S. Patent 6,713,464.

The Examiner requested new copies of Exhibits A and E filed January 18, 2008 since the copies scanned into the USPTO's records appear to have dark sections which make them difficult to read. Accordingly, enclosed herewith are new copies of Exhibits A and E.

Respectfully submitted,

Date: FEBRUARY 19, 2008 BY: 

Joseph A. Coppola
Reg. No. 38,413

KENYON & KENYON
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
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PTO/SB/26 (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 6,858,650 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 38,413

Signature — February 19, 2008 (Date)

Joseph A. Coppola, Reg. No. 38,413
Typed or printed name

(212) 425-7200
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

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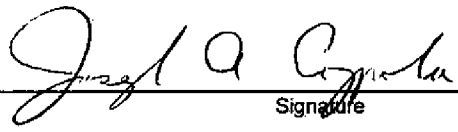

Signature — February 19, 2008 Date

Joseph A. Coppola, Reg. No. 38,413
Typed or printed name

(212) 425-7200
Telephone Number

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PTO/SB/25 (07-06)
Approved for use through 09/30/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional)
12961/46103

In re Application of: Claus MEESE, et al.

Application No.: 11/201,756

Filed: August 10, 2005

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

The owner*, SCHWARZ PHARMA AG, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 10/533,683, filed on April 26, 2005, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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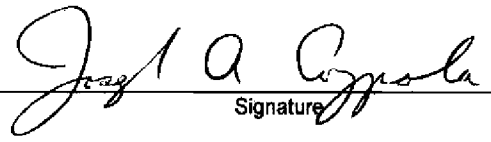

Signature — February 19, 2008 (Date)

Joseph A. Coppola, Reg. No. 38,413
Typed or printed name

(212) 425-7200
Telephone Number

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PTO/SB/25 (07-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 12961/46103

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Application No.: 11/201,756

Filed: August 10, 2005

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EXHIBIT A

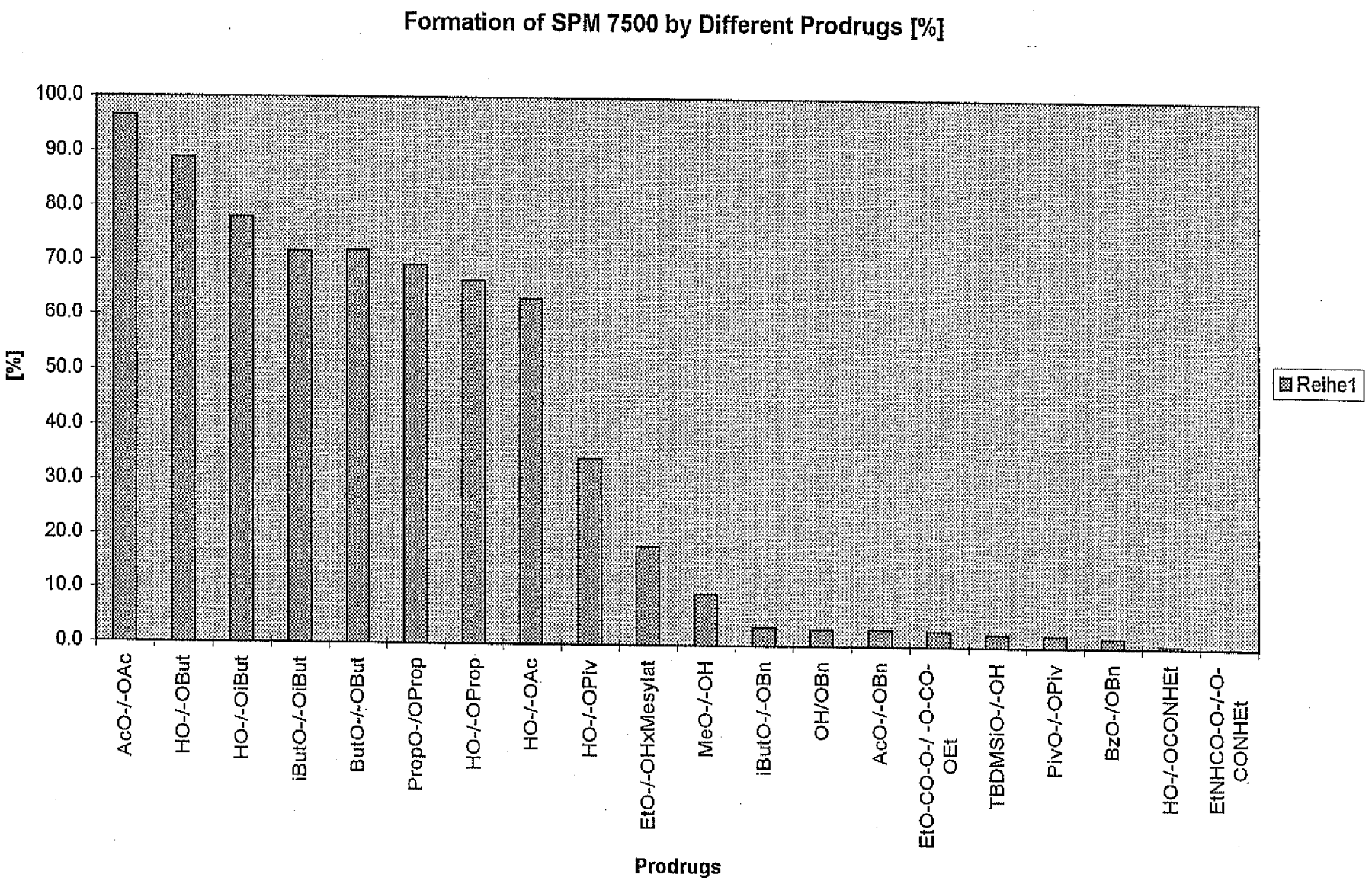


EXHIBIT E

SCHWARZ BIOSCIENCES	FORMULATION & TECHNOLOGY REPORT	Date 09.04.02
		Project No. Incontinence
		Page 1 of 16
TITLE **TDS for the treatment of incontinence, part IV: Delivery of Fesoterodine related prodrugs CONFIDENTIAL**		Report No. 32

1. SUMMARY

The report describes in vitro skin permeation characteristics of transdermal delivery systems (TDS) containing Fesoterodine related prodrugs from the SPM907 series. Test samples were prepared by either lab-scale solvent coating or hot-melt processing. Patches were tested by means of flux rates across hairless mouse skin, selected samples were subsequently investigated in the LACDR human skin model.

Initial experiments were performed in 1998/99 with TDS containing racemic mixtures of different produgs. While good drug permeation across mouse skin was found, flux rates across human skin were surprisingly low.

Due to the availability of pure enantiomers some of the prodrugs were reinvestigated in this feasibility study to find out the reason for low human skin permeation. The old flux data across mouse skin could be confirmed and in some cases increased. The low human skin permeations were found to be caused by the LACDR skin model setup. In this model the fresh human skin has to be supported by an additional synthetic membrane. The fresh skin most probably led to partial drug hydrolysis and/or protonation, while the supportive silicone membrane used is known to be impermeable for charged molecules. Replacing this membrane with a dialysis membrane increased the measured flux rates across human skin by a factor of at least 4 to 6. Therefore, the change to the human skin-dialysis membrane composite represents a more realistic estimation of the potential in vivo performance.

Besides the already reported free base of Fesoterodine, the diacetic acid ester prodrug seems to be a suitable transdermal candidate based on these new in vitro flux data.

Distribution: Original PH DOK
F&T, PHA, TS, TT, PH REG, IPM (AS)
Summary only: PCD, PH TOX, BA, MOBI, SIL, ILF

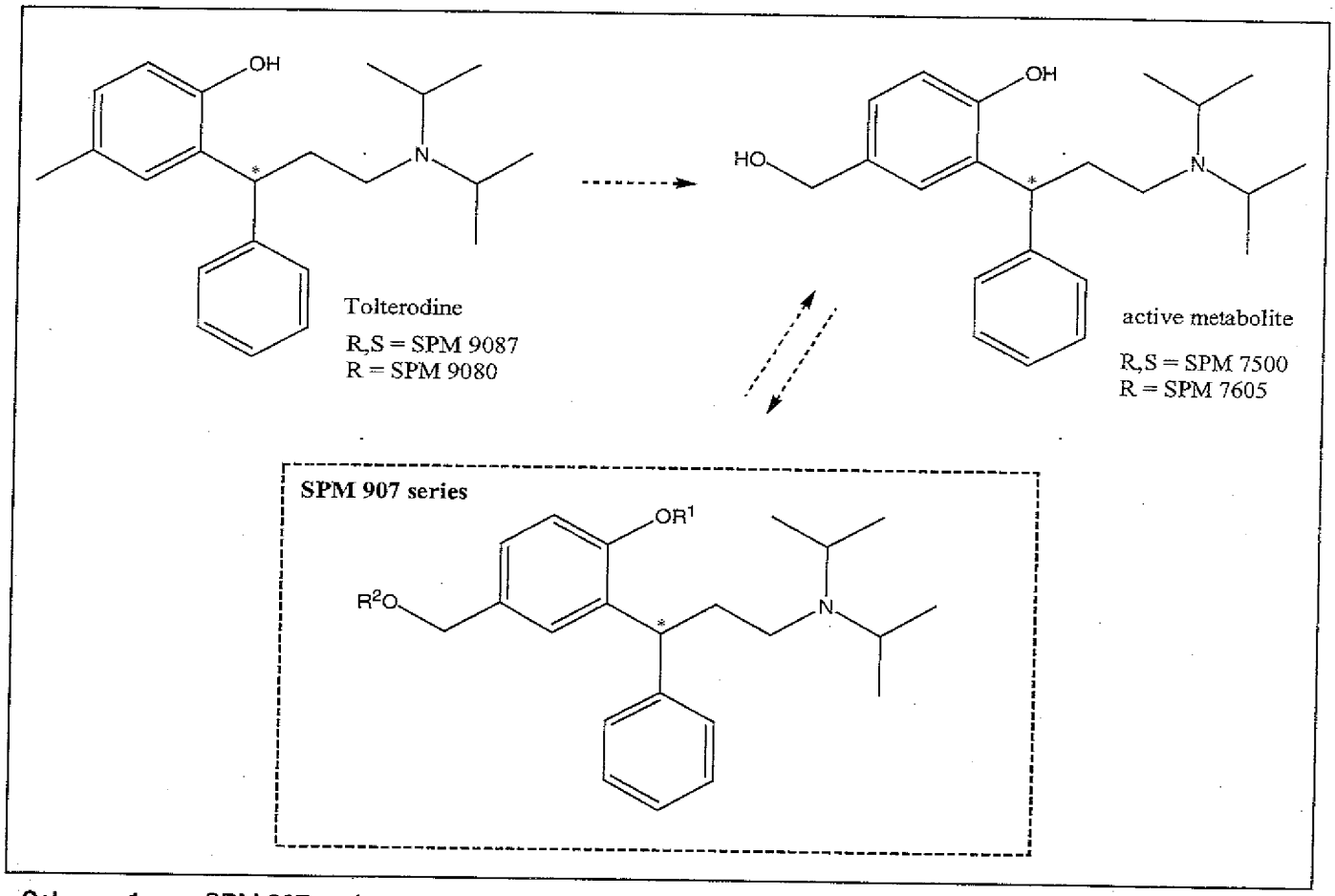
Key words:
Fesoterodine, SPM907 prodrugs, skin permeation in vitro, mouse skin, human skin

	Name	Signature	Date
Author			19.08.02
Head of TS	Dr. A. Breitenbach		
Reviewed by			20.08.02
Head of TT	Dr. H.-M. Wolff		
Approved by			20.08.02
Head of F&T	M.C.F. Hannay		

CONTENTS

2. INTRODUCTION AND OBJECTIVES

It is well known, that the hydroxy metabolite of Tolterodine is equipotent to the parent drug [1]. Therefore, several ester prodrugs of this metabolite, the SPM 907 series (scheme 1 and table 1) were synthesized by SIL [2] and subsequently tested for their ability to be delivered transdermally.



Scheme 1: SPM 907 series

Table 1: Assignment of some prodrugs of the SPM 907 series

R^1	R^2	R,S racemic mixture	R enantiomer
H	H	SPM 7500	SPM 7605
H	iBut	SPM 7504	fumarat salt = SPM 8272 = **Fesoterodine** SPM 8224 = **free base of Fesoterodine**
iBut	iBut	SPM 7502	SPM 7675
Ac	Ac	SPM 7501	SPM 8302

iBut → iso-butyric acid ester, Ac → acetic acid ester

Initial experiments performed in 1998/99 with racemic mixtures of the prodrugs revealed that they can be embedded into a solvent coated acrylic based TDS and that most of them possess the ability to permeate across hairless mouse skin with suitable flux rates. But, surprisingly, in many cases only low flux rates across human skin in the LACDR skin model [3] were found.

Due to the availability of pure enantiomers and a broader variety of patch compositions some of the prodrugs were re-investigated to find out the reason for low human skin permeation. Therefore, lab-scale batches of hot-melt and solvent coated patches were prepared and initially tested in a mouse skin model. Subsequently, some of the patches were investigated in the LACDR human skin model.

3. MATERIALS AND METHODS

For a detailed description of the experiments refer to the batch documentation.

Hot-melt patches (exemplary): 8 g of a preformed silicone adhesive were weighed into a beaker and tempered at 160°C for ca. 20 min to achieve a homogenous melt. 0.5 g of inner phase polymer (e.g. poly(ethylene oxide) and 1.5 g of drug were added. After tempering at 160°C for additional 5 min the mixture was homogenized manually and further processed on the pre-tempered Chill-Roll (120°C, 250 µm) for lamination.

5 cm^2 patches were isolated by manual punching followed by determination of the average patch weight (n=10). Finally, patches were sealed individually in pouches.

Mouse Skin Model (PHA): according to OBU0469.ABV100, rev. 00 (1998) with an active diffusion area of 2.55 cm^2, a phospate buffer acceptor phase at pH 6.2 and a temperature of 32°C, n=3

Human Skin Model (LACDR):
according to H. Tanojo et al. , J. Control Rel. 45 (1997) 41-47.
skin from abdomen with a thickness of approx. 250 µm, flux experiment: acceptor phase: PBS, pH= 6.2, temperature: 32ºC, diffusion cells with spiral groove (8 cells), groove area: 0.552 cm^2, dialysis membrane used as separator between skin and acceptor phase
flux: 5 ml/hour PBS, experiment runs for 72 hours, sampling cycle: 3 hours

Analytical Methods (PHA): refer to certificates of analysis

Data Analysis: sigmoidal Bolzmann and linear fit: Microcal Origin 6.0

4. RESULTS AND DISCUSSION

Racemic mixtures of the prodrugs (review of historic data)

Thirteen patch batches containing different racemic prodrugs of the SPM907 series as well as Tolterodine and Tolterodine prodrugs were initially embedded into acrylic-type polymers by a lab-scale solvent coating procedure. Tributyl citrate was added as plasticizer. All patches were investigated in both, the internal hairless mouse skin model and the LACDR human skin model. Table 2 summarizes some of the re-calculated former data.

Table 2: Solvent coated patches (with a theoretical drug content of 15% (w/w))

No	Lot No (Ch.B.)	Lot No (old)	Drug (SPM Code)	Permeation [1] Mouse Skin (n=4) [µg/(cm² 24h)]	Permeation [1,2] Human Skin [µg/(cm² 24h)]	Mouse : Human Skin Perm. Ratio
1	20002006	INZ 003	Di-iBut (7502)	155.54	43.64 / lag time ~14 h	3.56
2	20002008	INZ 005	iBut (7504)	496.87 [3]	193.31 / lag time ~34 h	2.57
3	20002005	INZ 002	Di-OH (7500)	689.21 [3]	5.96 / lag time ~38 h	115.64
4	20002014	INZ 011	Di-Ac (7501)	363.26 [3]	45.10 / lag time ~11 h	8.05

1) in case of SPM907 prodrugs re-calculated as permeation of active metabolite Di-OH (SPM 7500)

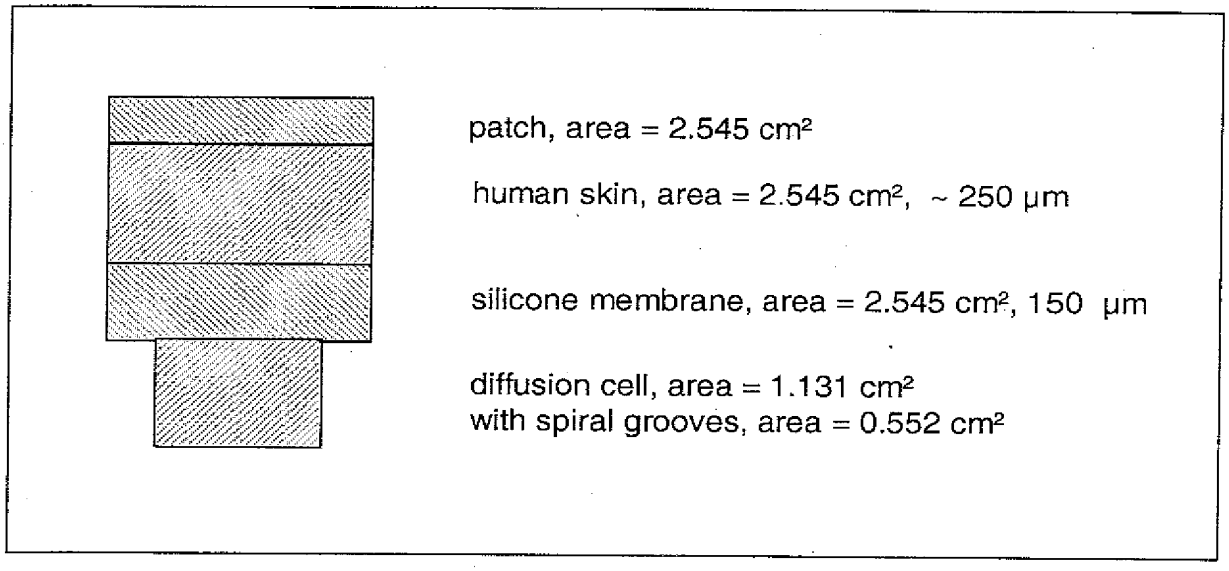
2) in case of SPM907 prodrugs calculated without consideration of the (low) amounts of hydrolysis products

3) non-linear release kinetics, calculated from the linear part in the period of 0-30 h

The observed permeation rates for most of the SPM907 prodrugs across mouse skin were suitably high. In case of the di-iso-butyric acid ester (No 1, table 2) steric hindrance most probably caused a lower value.

The flux rates across human skin decreased in the following order: iBut >> DiAc, DiBut >> DiOH. While the very low flux rate of SPM7500 (DiOH) could be caused by the hydrophilicity of this molecule, the low flux rates of SPM7501/2 (DiAc/DiBut) were surprising. To get a better understanding of these human skin permeation results a more detailed knowledge of the LACDR human skin model is necessary. In this model the skin is not in direct contact with the acceptor medium, since it has to be stabilized with an additional membran. A silastic sheeting (silicone membrane) was used in the oder experiments described above to support the skin (compare scheme 2).

Scheme 2: LACDR experimental setup



Due to this setup always two experiments have to be performed: one to determine the flux of the active across the supportive membrane and a second one to determine the flux across the 'composite' of human skin and supportive membrane. The obtained values of the barrier properties of the supportive membrane are used to correct the values of the second experiment.

In all experiments acceptable high flux rates for the SPM907 prodrugs across the supportive membrane were found (comp. Annex), although the permeability of the silicone membrane decreased in the following ranking order: Di-But > iBut > DiAc > Di-OH, possibly due to increasing hydrophilicity. Nevertheless, all values were high enough and therefore, acceptable for the determination of the barrier properties of the silastic sheeting.

From the data obtained in the experiments with the human skin - supportive membrane composite it can be stated, that a) the flux of the active metabolite (DiOH, No 3 table 2) was generally quite low and b) the flux of the racemic free base of Fesoterodine (iBut, No 2 table 2) would theoretically enable the delivery of nearly 4 mg/24 h from a 20 cm^2 patch across human skin.

Nevertheless, the partially extremely low flux rates found for the ester prodrugs indicate secondary processes taking place. Since in the LACDR model fresh human skin is used, it is likely that metabolic/enzymatic activity is still present. Thereby induced ester hydrolysis will immediately generate charged molecules, which are no longer able to permeate across the supportive membrane (compare next paragraph). In conclusion, these older data do not assess the human skin permeation of all SPM907 (pro)drugs accurately.

R-enantiomers

As already reported [4] Fesoterodine and some of the prodrug enantiomers were investigated by controlled melt embedding (temperature range of 25-150°C) to assess the drug excipient compatibility under hot-melt conditions. 1:1 mixtures of drug and excipient showed no signs of degradation under the test conditions enabling patch preparation by hot melt techniques.

SPM7605 (DiOH)

SPM7605 is the main hydrolysis product and active metabolite of Fesoterodine and related prodrugs from the SPM907 series. The colorless powder is characterized by a melting point in the range of ~101-102°C and a purity or more than 99%. More than 10 lab-scale batches of hot-melt patches were prepared without encountering any difficulties. Table 3 summarizes some of the results obtained in the mouse skin model.

Table 3: SPM7605 hot melt patches

No	Lot No. (Ch.B.)	PSA	Theo. Drug Loading [% w/w]	Mouse Skin Perm. [µg/(cm² 24 h)]
1	20008029	SxS	10	261.55 [1)]
2	20008030	SxS	10	274.32 [1)]
3	20106045	EVA	15	220.87 [1)]
4	20106043	BioPSA/PEO	15	384.04 [1)]

1) non-linear release linetics, calculated from the linear part in the period of 0-30 h

SxS: styrene-block-copolymer, EVA = ethylene vinyl acetate copolymer,

BioPSA/PEO = silicone pressure sensitive adhesive containing additional 5% poly(ethylene oxide)

From these data it can be concluded that the flux rates of the pure enantiomer SPM7605 across mouse skin were still in a suitable range, although the observed values were generally lower than those obtained with the racemic mixture, SPM7500 (No 3 table 2). The most likely explanation is the difference of the patch compositions used.

No 4 (table 3) was investigated in the LACDR human skin model (for flux data comp. Annex). Already the flux across the supportive silastic sheeting was lower than across mouse skin, therefore, the flux across the composite of human skin plus membrane was negligible. The corrected value for human skin was found to be 2.3 µg/(cm² 24 h), again an approx. 95 times lower value compared to mouse skin, which is comparable to the former investigation (No. 3, table 2). With this experimental setup it was not possible to determine the flux of SPM7605 across human skin accurately. Due to a lack of capacity, no experiments with different supportive membranes were performed.

SPM8272 (OiBut/Fum; Fesoterodine) and SPM8224 (OiBut, free base of Fesoterodine)

The experiments with patches containing either Fesoterodine or the free base of Fesoterodine were already reported [5,6]. While the passive transdermal delivery of Fesoterotine seemed to be not suitable, very high flux rates of the free base of Fesoterodine across human skin make SPM8224 a very promising candidate for the transdermal treatment of overactive bladder.

SPM7675 (DiBut, di-iso-bytyric acid ester)

SPM7675, the di-iso-butyric acid ester of SPM7605 (DiOH = active metabolite of Fesoterodine), is an oil with a purity of approx. 95%. Due to low amounts of drug available, a lack of capacity and generally lower permeation rates only five patch batches were prepared and investigated by means of drug permeation across hairless mouse skin. In accordance with the former data obtained for the racemic micture, permeation rates in the range of 120 to 150 µg/(cm² 24h) were observed (data not shown). Since these in vitro mouse skin data were not in the therapeutic range, no further studies with SPM7675 were performed.

SPM8302 (DiAc, di-acetic acid ester)

SPM8302, the di-acetic acid ester of SPM7605 (DiOH = active metabolite of Fesoterodine) is an oil with a purity of approx. 95%. More than 25 different lab scale patch batches were prepared (comp. Annex). The drug could be incorporated into the complete range of available pressure sensitive adhesives covering silicones, acrylates, ethylene vinyl acetate copolymers as well as styrene-block-copolymers (comp. Annex). Fig. 1 gives an example of the obtained flux rates across mouse skin.

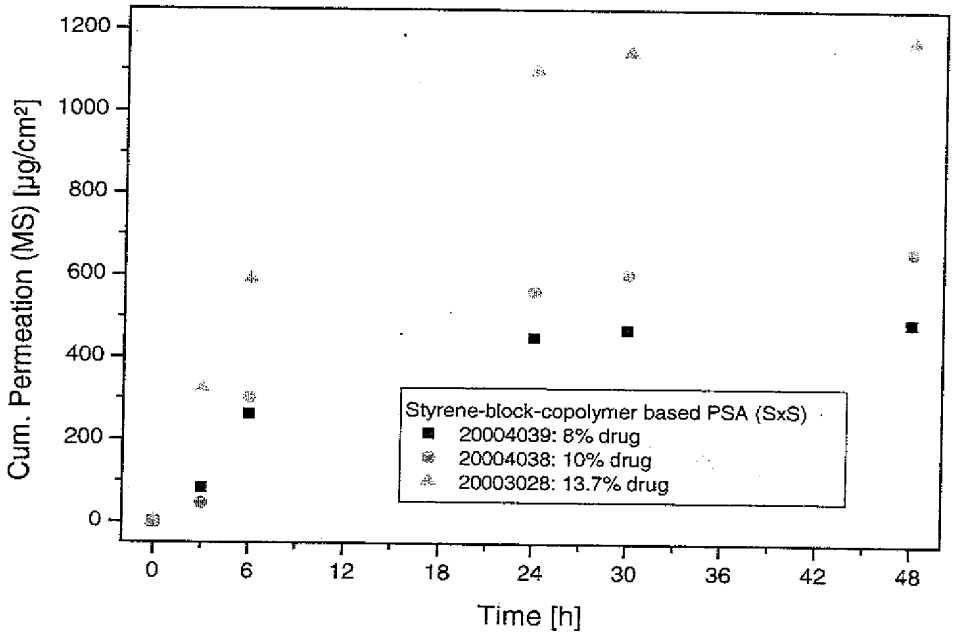


Fig. 1a: **Skin permeation across mouse skin** (calculated as release of active metabolite), batches prepared by lab scale hot melt processing by incorporating 8, 10 and 13.7% (w/w) SPM8302 into Dermagel 10127-113-3, a styrene-block-co-polymer based adhesive from National Starch & Chemical.

Very high flux rates, increasing with increasing drug loading, were observed (fig. 1a).

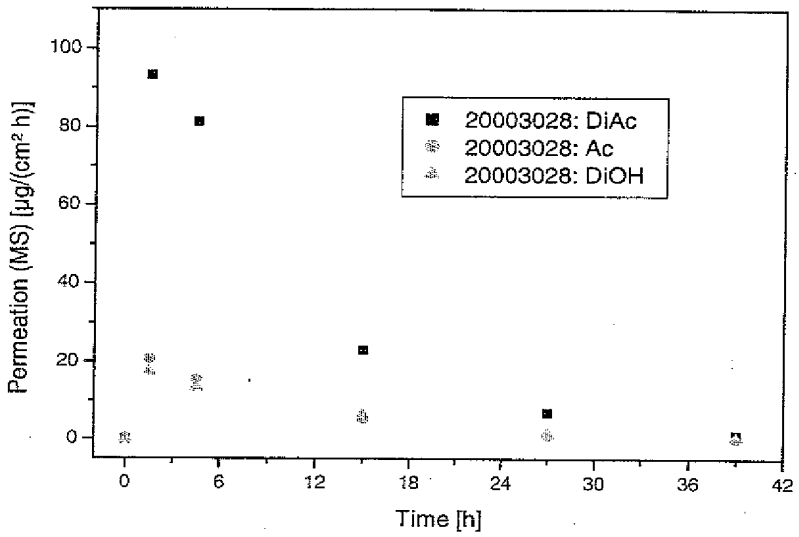


Fig. 1b: Differiential skin permeation as a function of different hydrolysis products

As outlined in fig. 1b initially ca. 20% of the drug were detected as monoester and additional 20% as active metabolite in the aceptor medium indicating the rapid hydrolysis of the prodrug once in contact with skin and/or water.

Two different samples were investigated in the LACDR human skin model. Fig. 2 outlines the initial permeation results which were in accordance with the former evaluation.

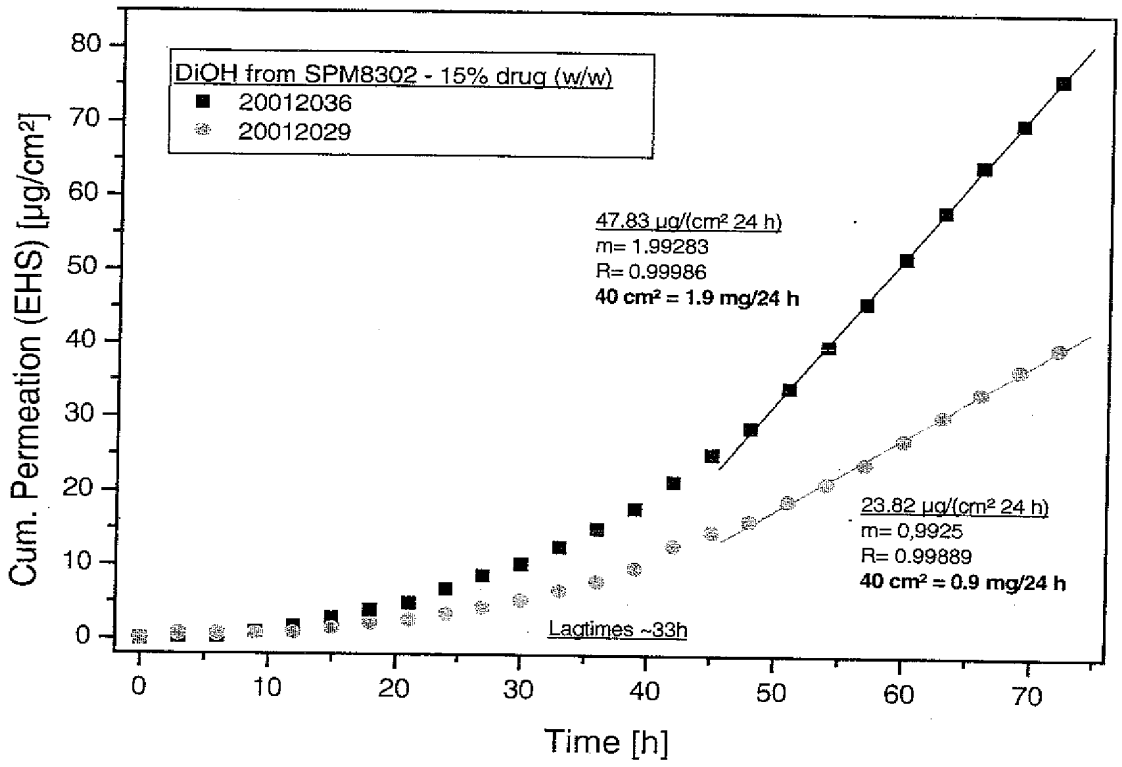


Fig. 2: Cumulative permeation across excised human skin (values corrected with the flux barrier of the supportive silastic sheeting), batches prepared by lab scale solvent coating (20012036: 15% (w/w) drug in acrylic type adhesive, National Starch & Chemical Duro Tak 387-4287) and hot melt processing (20012029: 15% (w/w) drug in silicone based adhesive (BioPSA, Dow Corning) plus additional inner phase polymer (10% (w/w) Vinapas = poly(viny acetate)))

Due to the very high permeation results across mouse skin, the flux rates across human skin seemed to be too low. Since always fresh human skin is used in the LACDR model, a likely explanation could be that remaining enzymatic activity in the skin led to fast drug hydrolysis and the generation of charged molecules. Unfortunately, the skin supporting silastic sheeting

is impermeable to charged molecules. This effect will of course only be visible in the experiment with the composite of human skin supported by the silastic sheeting, which explains, why always high permeation rates were found when testing the synthetic membrane alone.

An experimental change by replacing the supportive membrane with a dialysis membrane which is not impermeable to charge moleculaes, significantly improved the results as outlined in fig. 3.

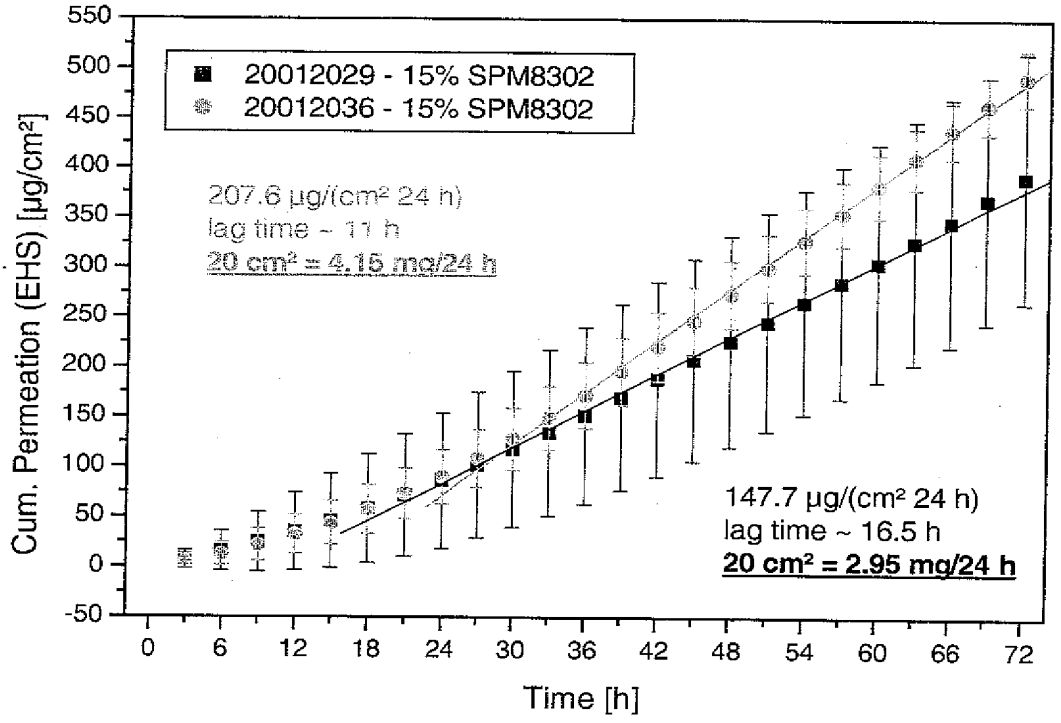


Fig. 3: Cumulative permeation across excised human skin (plus dialysis membrane, calculated as permeation of active metabolite)

Four to six times higher fux rates indicated that this experimental setup represented a more reasonable assessment of the flux across human skin. Moreover, the values found for batch 20012036 indicated the promising potential of SPM8302 to be used for the treatment of

overactive bladder. Patches with sizes in the range of 20 to 40 cm^2 could theoretically deliver 4 to 8 mg/24 h which is the current range of the oral Fesoterodine formulation.

CONCLUSIONS

After having already demonstrated the promising transdermal potential of SPM8224, the free base of Fesoterodine, here the alternative use of several different Fesoterodine related prodrugs from the SPM907 series was investigated.

Based on the results obtained, only SPM8302 could be used as alternative since its flux rates across human skin were found to be sufficient for the treatment of overactive bladder with patch sizes in the range of 20 to 40 cm^2 (equal to delivery of ca. 4 to 8 mg in 24 h). These data have to be confirmed in vivo.

ANNEX 1

Copies of the Certificates of Analysis

(signed originals stored at PH DOK)

SPM 8302	SPM 7605	SPM 8272	SPM 7675	SPM 8224
Ch.B.	Ch.B.	Ch.B.	Ch.B.	Ch.B.
20008079	20008039	20008042	20002029	20111080
20008078	20008038	20008041	20002032	20111085
20008060	20008037	20008040	20002030	20111086
20008059	20008036	20004054	20002027	20111087
20008057	20008032	20004053	20002021	20111095
20008056	20008031	20003034		20201027
20008055	20008030	20002052		20201028
20008033	20008029	20002051		
20006011	20106045	20002050		
20006010	20106043	20002046		
20006009		20002042		
20004058		20002041		
20004057		20002040		
20004056		20002037		
20004055		20002031		
20004041		20002020		
20004040		20002019		
20004039		20002018		
20004038		20104034		
20003052		20104035		
20003051		20104037		
20003050		20104038		
20003033		20106061		
20003032				
20003031				
20003030				
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20012026				
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20012028				
20012029				
20012030				
20012036				

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ 002
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN004A-M	Analysendatum :	06.-09.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 8 Wochen TK-Schrank SKH-1o
1=160µm R ; 2=146µm R 34,3 ; 3=147µm R ,4=149µm R 30,7g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit [h]	di-OH-Base 1	2	3	4	MW	SD	add.
3	518,7	326,5	306,7	686,2	**459,5**	**178,8**	459,5
6	753,0	549,2	483,2	648,5	**608,4**	**117,9**	1068,0
24	2868,5	2501,4	2287,0	2634,6	**2572,9**	**243,6**	3640,9
30	778,9	685,1	677,4	742,6	**721,0**	**48,3**	4361,8
48	1641,8	1542,4	1593,5	1524,1	**1575,4**	**53,1**	5937,3
54	421,0	429,9	457,6	385,8	**423,5**	**29,6**	6360,8
72	896,7	1013,1	1153,2	851,3	**978,6**	**134,9**	7339,4

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	971,5	µg
Regressionskoeffizient (m) =	2,3	µg/h
Korrelationskoeffizient (r) =	0,0744	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ003
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN006A-F	Analysendatum :	13.-17.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 1 Woche TK-Schrank SKH-1♂
1=117µm R ; 2=115µm ; 3=124µm R ,4=113µm R 33,4g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert
Zusammensetzung : SPM 7502 ; SPM 7504 ; SPM 7500

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM 7502						SPM 7504		SPM 7500		Summe	
[h]	1	2	3	4	MW	SD	MW	SD	MW	SD	MW	kumu.
3	41,3	63,8	55,1	77,3	**59,4**	15,1	**75,3**	8,4	**15,3**	1,4	**149,9**	149,9
6	128,8	141,2	143,3	162,9	**144,0**	14,1	**75,3**	10,6	**10,4**	0,7	**229,7**	379,7
24	638,5	47,2	576,7	754,6	**504,2**	313,5	**336,7**	81,5	**68,8**	32,5	**909,8**	1289,5
30	0,0	0,0	0,0	0,0	**0,0**	0,0	**0,0**	0,0	**8,5**	0,9	**8,5**	1297,9
48	603,9	828,4	654,7	676,6	**690,9**	96,6	**115,4**	16,0	**49,5**	5,5	**855,8**	2153,7
54	198,0	231,0	223,8	218,6	**217,8**	14,2	**30,0**	9,3	**11,2**	1,7	**259,1**	2412,8
72	515,7	566,3	559,5	559,4	**550,2**	23,2	**66,4**	6,1	**39,8**	4,0	**656,5**	3069,2

MW = Mittelwert SD = Standardabweichung MW = Mittelwert SD = Standardabweichu

Achsenabschnitt (b)= 244,6 µg
Regressionskoeffizient (m 5,7 µg/h
Korrelationskoeffizient (r) 0,4029

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ005
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN008A-F	Analysendatum :	13.-17.07.98
ABV vom :	----------		

Bemerkungen: 8 Wochen lebend 1 Woche TK-Schrank SKH-1♂
1=109µm R ; 2=116µm ;R 26,9 ; 3=147µm R ,4=136µm R 25,1g
Temperatur 32°C , Puffer pH 6.2 nach K.T.
Die Proben wurden nicht aufkonzentriert
Zusammensetzung : SPM 7504 ; SPM 7500

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM 7504						SPM 7500		Summe	
[h]	1	2	3	4	MW	SD	MW	SD	MW	kumu.
3	506,3	587,1	692,3	374,7	**540,1**	134,0	**29,8**	5,4	**569,8**	569,8
6	617,1	621,9	654,8	472,7	**591,6**	81,0	**24,6**	2,0	**616,2**	1186,1
24	2244,7	2178,9	2340,2	2040,9	**2201,2**	125,7	**125,6**	10,4	**2326,7**	3512,8
30	499,6	520,7	500,9	510,6	**507,9**	9,8	**30,2**	2,6	**538,1**	4051,0
48	948,9	1058,0	911,8	1027,1	**986,5**	67,7	**89,4**	10,0	**1075,8**	5126,8
54	231,8	288,4	213,7	271,2	**251,3**	34,5	**24,2**	3,0	**275,5**	5402,3
72	476,0	675,3	414,7	591,3	**539,3**	116,5	**50,6**	7,7	**589,9**	5992,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	999,2	µg
Regressionskoeffizient (m) =	-4,2	µg/h
Korrelationskoeffizient (r) =	-0,1562	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

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Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-LM-TDS	Ch.-B.:	INZ 011
Sollgehalt :	7,50 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN031A-C	Analysendatum :	04.12.98
ABV vom :	analog OBU 0469.100		

Bemerkungen: 10 Wochen lebend 5 Wochen TK-Schrank SKH-1♂
1=130µm R ; 2=128µm R 32,1 ; 3=149µm R ,4=154µm R 31,8g
Die Proben wurden nicht aufkonzentriert und nicht filtriert

Tabelle der kumulierten Freisetzung in µg / 5 cm²

Zeit	SPM_7501						SPM_7500 zu SPM_7501		MW
[h]	1	2	3	4	MW	SD	MW	SD	add.
3	363	582	237	624	**452**	**183**	**25**	**7**	**476**
6	765	1046	615	1235	**915**	**278**	**43**	**9**	**959**
24	2240	2658	2106	3086	**2523**	**443**	**189**	**21**	**2711**
30	2638	3065	2531	3539	**2943**	**459**	**212**	**21**	**3155**
48	2857	3277	2770	3768	**3168**	**457**	**295**	**19**	**3463**
54	3200	3564	3124	4014	**3476**	**407**	**327**	**18**	**3802**
72	3721	3989	3635	4317	**3916**	**307**	**386**	**17**	**4302**

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	848,3	µg
Regressionskoeffizient (m) =	48,3	µg/h
Korrelationskoeffizient (r) =	0,9403	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h - 72h)

19.08.02

Datum/PH-A Sachbearbeiter(in) Projektgruppenleiter

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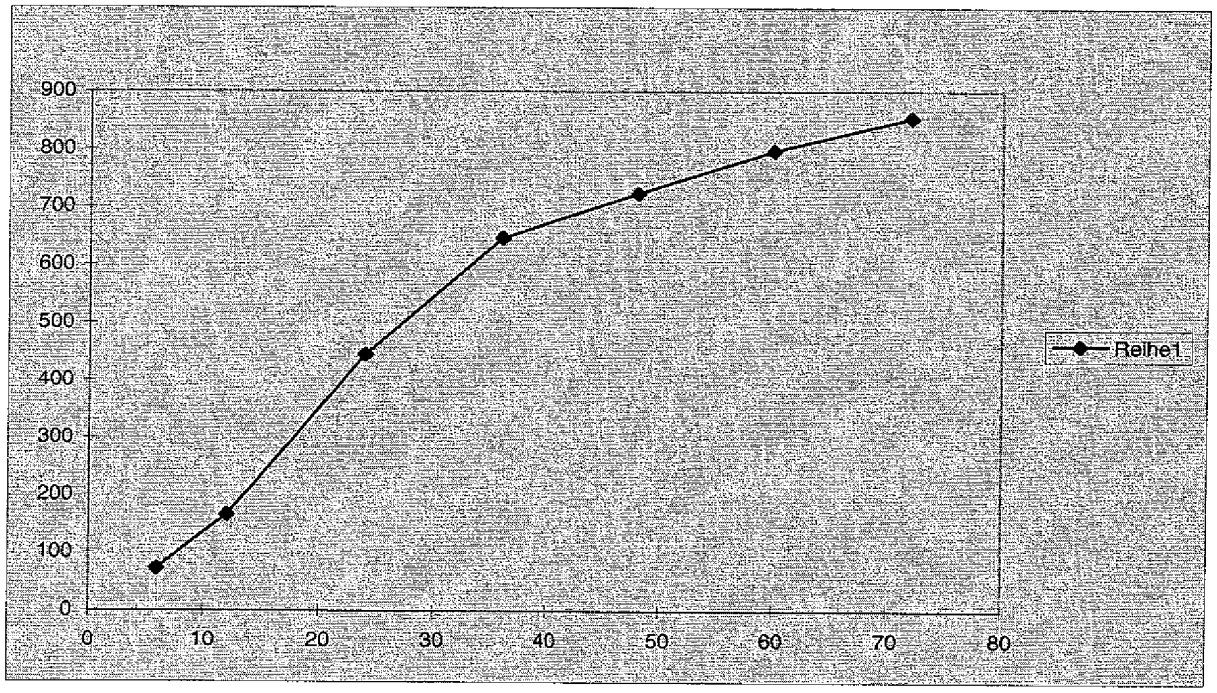
Auswertung Wirkstoff SPM 7500

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**0,00**	0,00	0,00	**0,00**
12	**0,00**	0,00	0,00	**0,00**
24	**0,00**	0,00	0,00	**0,00**
36	**0,00**	0,00	0,00	**0,00**
48	**2,39**	0,51	21,41	**2,39**
60	**3,04**	0,70	23,09	**5,43**
72	**2,85**	2,24	78,81	**8,27**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**72,52**	0,00	0,00	**72,52**	0,00	0,00
12	**93,11**	0,00	0,00	**165,63**	0,00	0,00
24	**279,19**	0,00	0,00	**444,82**	0,00	0,00
36	**200,90**	0,00	0,00	**645,72**	0,00	0,00
48	**76,57**	0,00	0,00	**722,28**	0,00	0,00
60	**74,45**	0,00	0,00	**796,73**	0,00	0,00
72	**56,92**	0,00	0,00	**853,65**	0,00	0,00



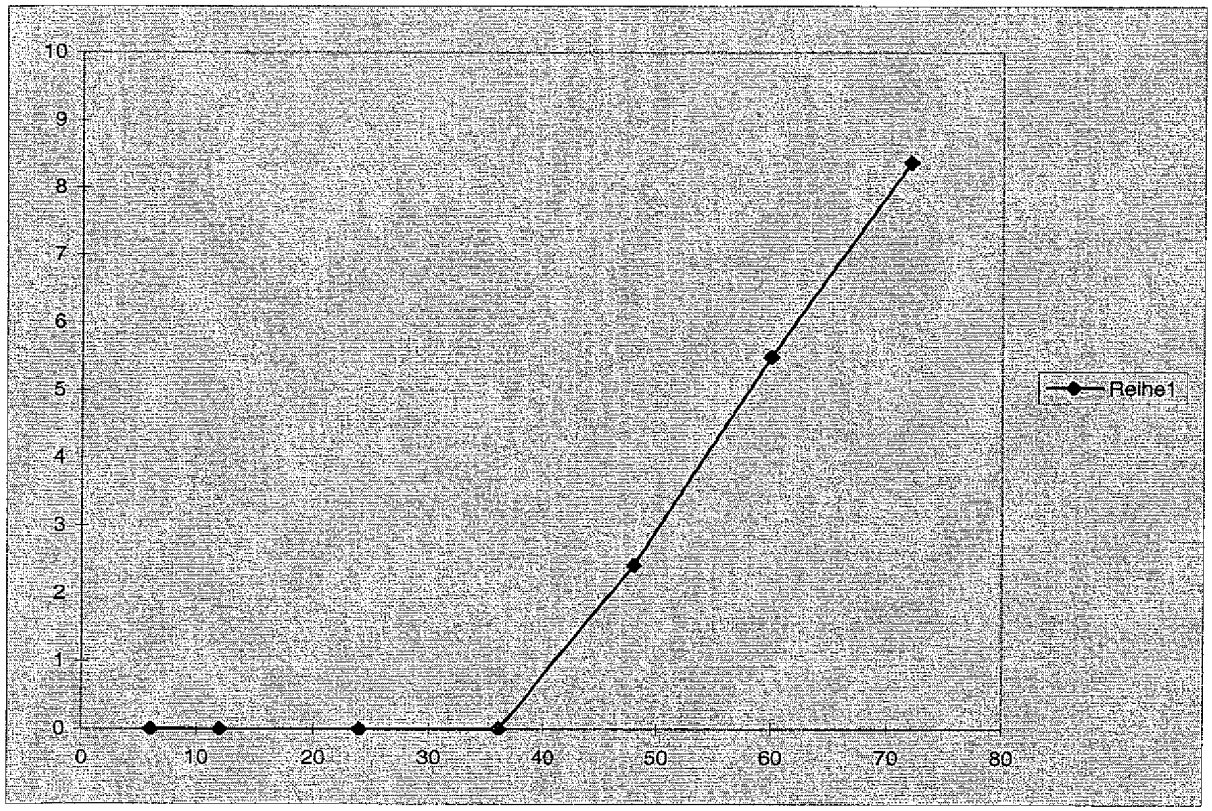
für SIL kumuliert
linearer Bereich von 6-24 h
lineare Regression

r^2	0,994665	
m	19,65	[µg/cm²*h]
b	-51,03	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 117,91

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 235,82

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	0,00	0,00
36	0,00	0,00
48	2,41	2,41
60	3,08	5,49
72	2,88	8,37



Hautpermeation des Wirkstoffs SPM 9080

linearer Bereich von 48-72h

lineare Regression

r^2	0,999632	
m	0,25	[µg/cm²*h]
b	-9,47	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 9080 über 24 h von:

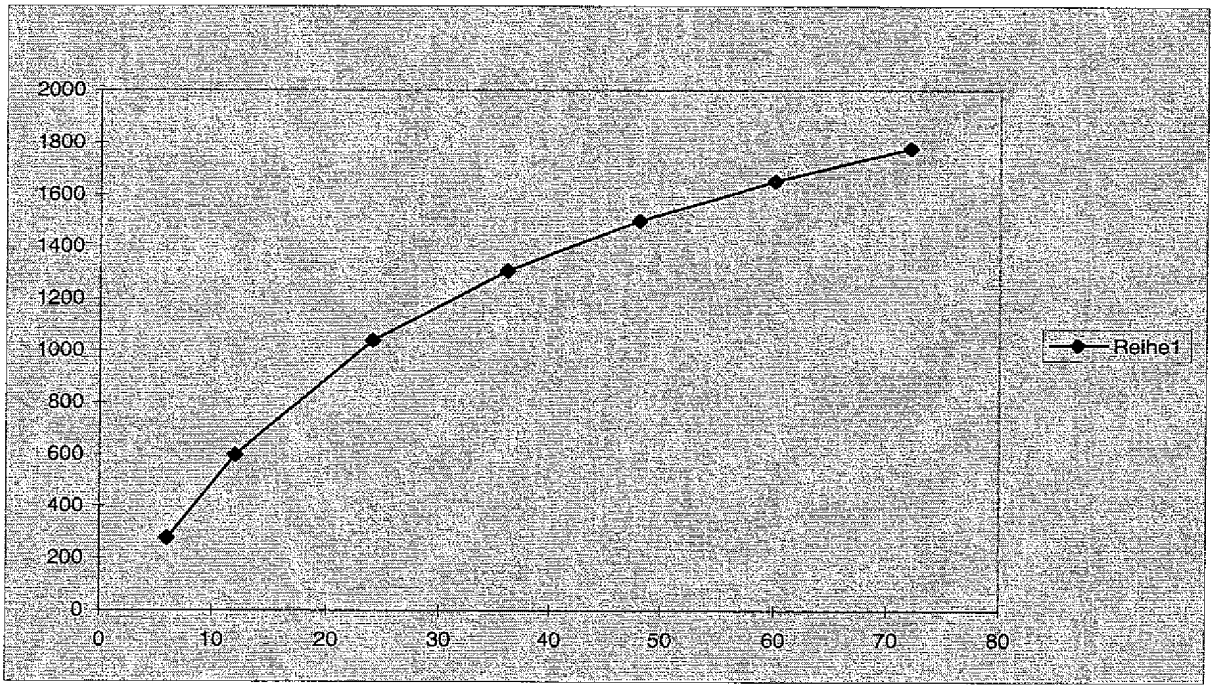
5,96 µg/cm²*24 h

lag-time: **38,1 h**

Auswertung Wirkstoff SPM 7502

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**2,30**	0,00	0,00	**2,30**
12	**7,04**	0,00	0,00	**9,34**
24	**25,23**	0,00	0,00	**34,57**
36	**31,47**	0,00	0,00	**66,04**
48	**31,07**	0,00	0,00	**97,11**
60	**30,40**	0,00	0,00	**127,50**
72	**27,08**	0,00	0,00	**154,58**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**276,75**	66,89	24,17	**276,75**	66,89	24,17
12	**320,76**	32,52	10,14	**597,51**	99,41	16,64
24	**440,59**	26,58	6,03	**1038,09**	72,83	7,02
36	**268,02**	8,75	3,26	**1306,12**	81,58	6,25
48	**192,03**	35,40	18,44	**1498,15**	46,17	3,08
60	**153,48**	19,27	12,56	**1651,64**	26,90	1,63
72	**126,51**	7,68	6,07	**1778,14**	19,22	1,08



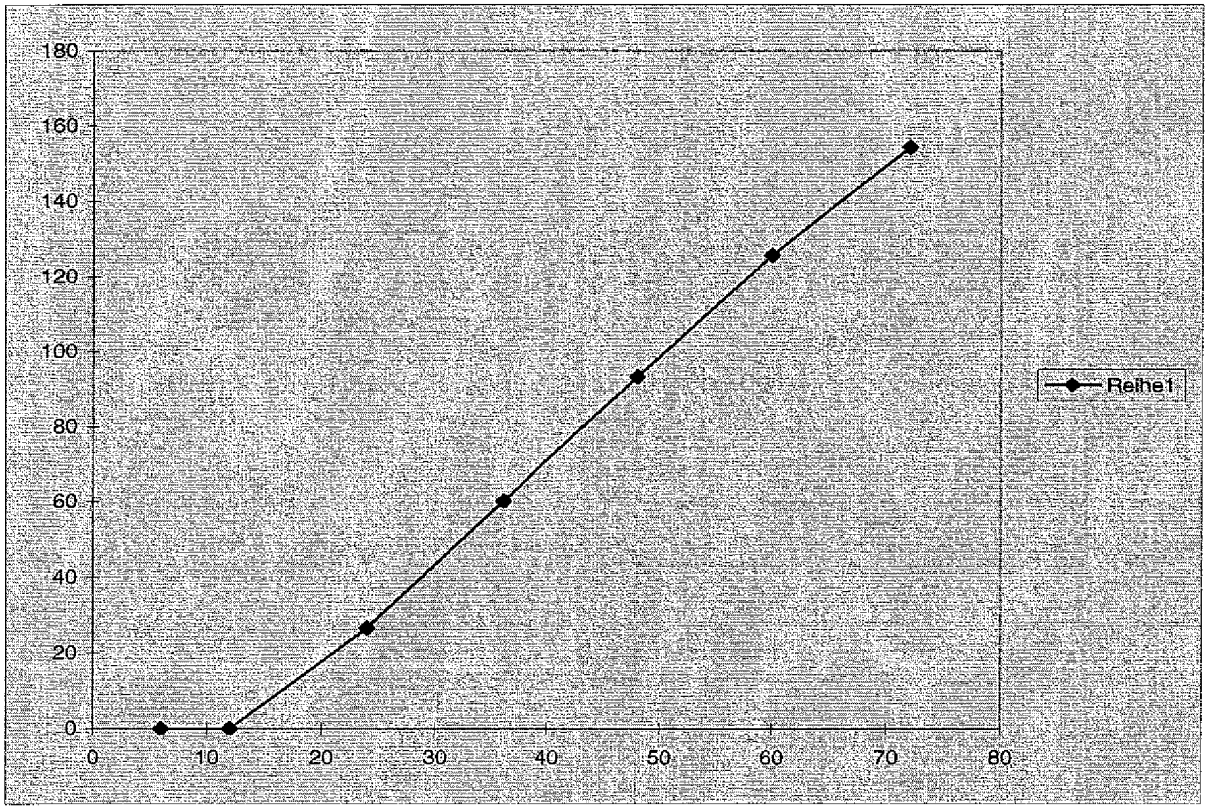
für SIL kumuliert
linearer Bereich von 6-72 h
lineare Regression

r^2	0,931582	
m	41,50	[µg/cm²*h]
b	56,46	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 249,00

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 497,99

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	26,58	26,58
36	33,59	60,17
48	33,14	93,31
60	32,37	125,68
72	28,63	154,32



Hautpermeation des Wirkstoffs SPM 7502

linearer Bereich von 24-72h

lineare Regression

r^2	0,999095	
m	2,67	[µg/cm²*h]
b	-36,38	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7502 über 24 h von:

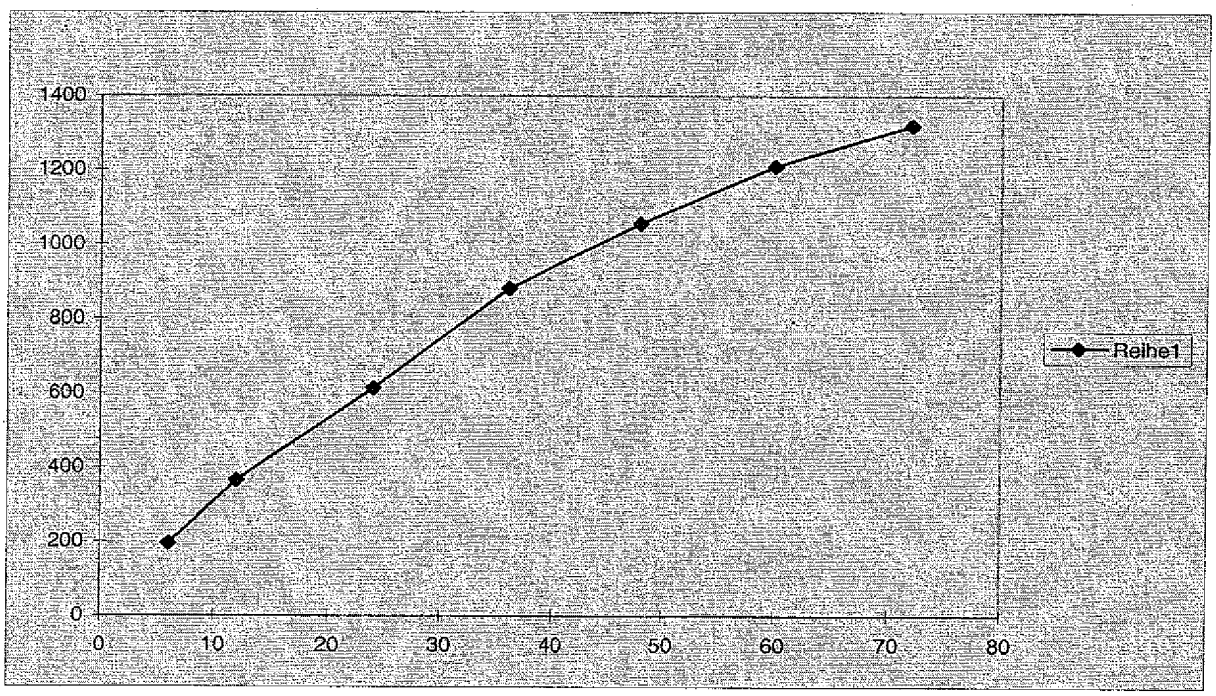
64,20 µg/cm²*24 h

lag-time: **13,6 h**

Auswertung Wirkstoff SPM 7504

	Haut + SIL			Haut + SIL kumuliert
Zeit [h]	mean	SD	VC	mean
6	**0,00**	0,00	0,00	**0,00**
12	**0,00**	0,00	0,00	**0,00**
24	**3,73**	0,00	0,00	**3,73**
36	**8,73**	0,00	0,00	**12,46**
48	**7,16**	0,00	0,00	**19,62**
60	**4,22**	0,00	0,00	**23,84**
72	**6,77**	0,00	0,00	**30,62**

	SIL			SIL kumuliert		
Zeit [h]	mean	SD	VC	mean	SD	VC
6	**195,02**	80,08	41,06	**195,02**	80,08	41,06
12	**170,12**	53,21	31,28	**365,13**	133,30	36,51
24	**248,29**	68,26	27,49	**613,43**	201,56	32,86
36	**267,65**	82,65	30,88	**881,08**	284,21	32,26
48	**174,81**	11,33	6,48	**1055,89**	295,54	27,99
60	**154,31**	28,40	18,40	**1210,19**	323,94	26,77
72	**109,97**	66,64	60,59	**1320,17**	390,58	29,59



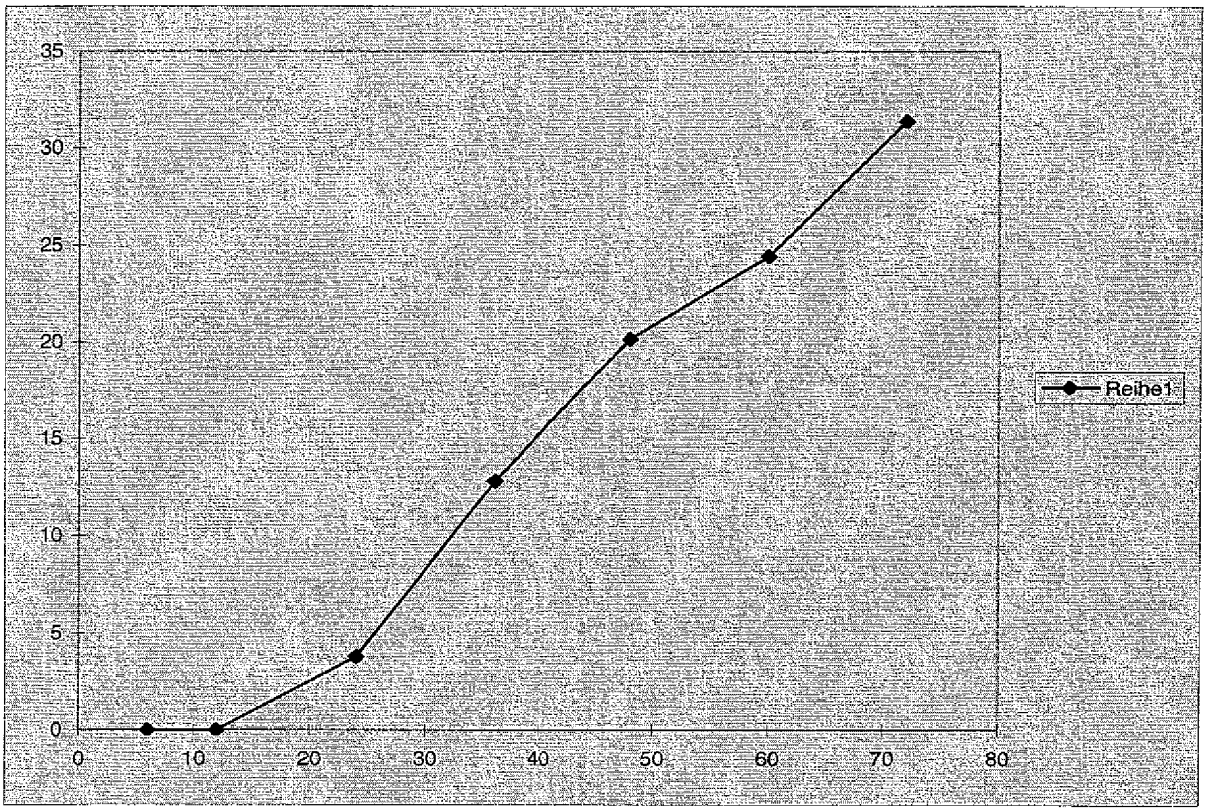
für SIL kumuliert
linearer Bereich von 6-72 h
lineare Regression

r^2	0,975393	
m	22,88	[µg/cm²*h]
b	70,87	[µg/cm²]

für ein 6 h Intervall ergibt sich ein mittlerer Wert von 137,28

für ein 12 h Intervall ergibt sich ein mittlerer Wert von 274,56

Zeit [h]	Haut mean	Haut kumuliert mean
6	0,00	0,00
12	0,00	0,00
24	3,79	3,79
36	9,01	12,80
48	7,35	20,15
60	4,29	24,44
72	6,94	31,38



Hautpermeation des Wirkstoffs SPM 7504

linearer Bereich von 24-72h

lineare Regression

r^2	0,986107	
m	0,56	[µg/cm²*h]
b	-8,22	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7504 über 24 h von:

13,37 µg/cm²*24 h

lag-time: **14,8 h**

Wirkstoff SPM 7501

Zeit [h]	Haut mean	Haut kumuliert mean
6	3,82	3,82
12	6,30	10,12
24	20,00	30,11
36	26,57	56,69
48	25,52	82,21
60	27,13	109,33
72	29,24	138,57

Metabolit SPM 7500

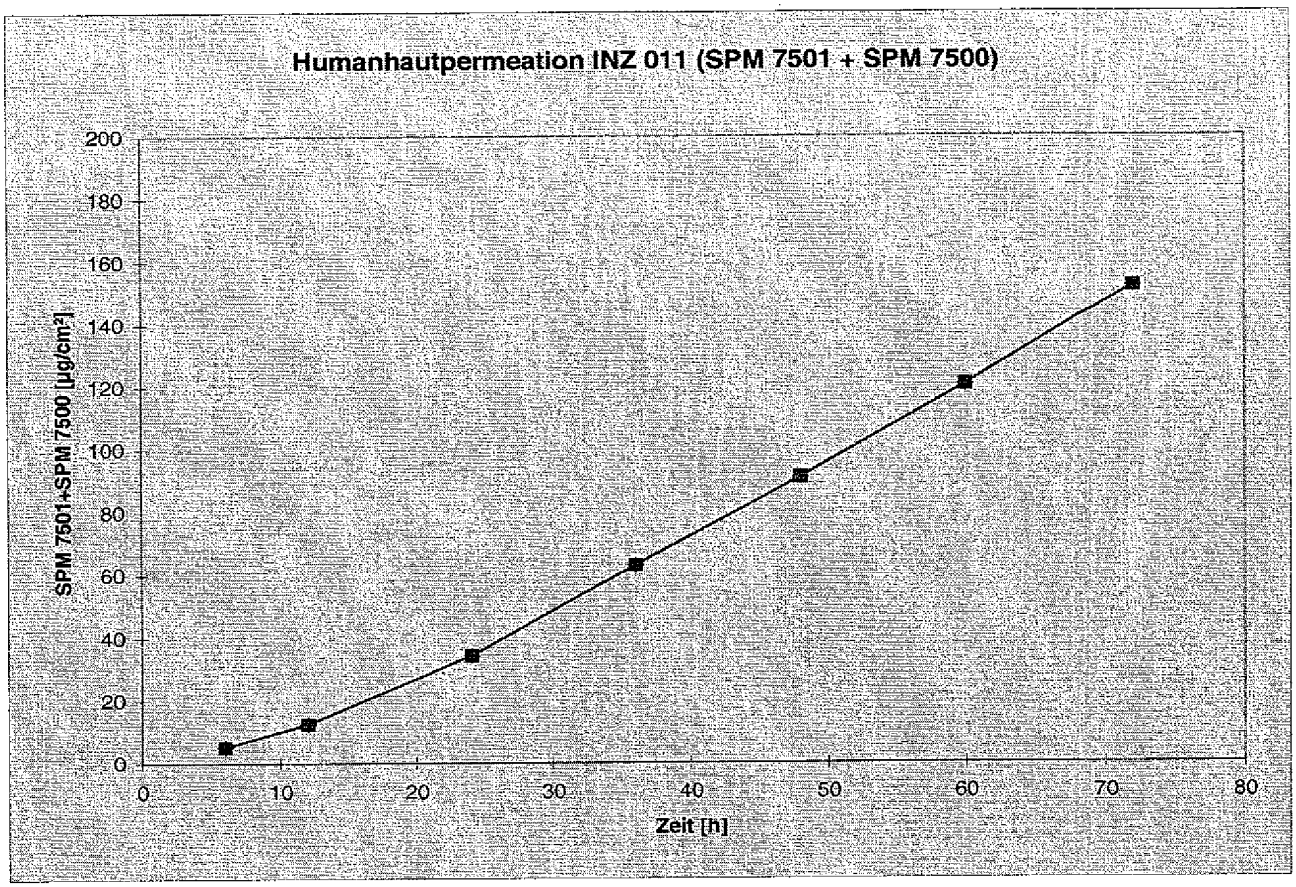
	Haut mean	Haut kumuliert mean
	1,07	1,07
	0,83	1,90
	1,54	3,43
	1,69	5,12
	2,01	7,13
	1,94	9,07
	1,83	10,90

Metabolit SPM 7500 umgerechnet in Wirkstoff SPM 7501

Zeit [h]	Haut mean	Haut kumuliert mean
6	1,33	1,33
12	1,03	2,36
24	1,92	4,28
36	2,11	6,39
48	2,51	8,89
60	2,41	11,30
72	2,28	13,58

Summe aus Wirkstoff SPM 7501 und Metabolit 7500

Zeit [h]	**Haut mean**	**Haut kumuliert mean**
6	**5,15**	**5,15**
12	**7,33**	**12,48**
24	**21,91**	**34,39**
36	**28,68**	**63,07**
48	**28,03**	**91,10**
60	**29,54**	**120,64**
72	**31,52**	**152,15**



Hautpermeation von SPM 7501 + SPM 7500

linearer Bereich von 24-72 h

r^2	0,999484959	
m	2,442	[µg/cm²*h]
b	-24,964	[µg/cm²]

Somit ergibt sich eine mittlere Freisetzungsrate an SPM 7501 + SPM 7500 über 24 h von:

58,6 µg/cm²/24 h

lag-time **10,2 h**

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM7605**	Ch.-B.:	20008029
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IB0773_MHP	Analysendatum :	17.08.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=170; 2=162 3=164, 30,3g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

mg DIOH / 5cm²					
Zeit [h]	1	2	3	**MW**	SD
3	0,34	0,17	0,28	**0,26**	0,09
6	0,64	0,44	0,56	**0,55**	0,10
24	1,60	1,53	1,56	**1,56**	0,04
30	1,83	1,78	1,81	**1,81**	0,02
48	2,27	2,30	2,34	**2,30**	0,03

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,28	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,98122	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM7605**	Ch.-B.:	20008030
Sollgehalt :		TDS- Fläche :	5 cm^2
Analysen-Nr:	IB0773_MHP	Analysendatum :	17.08.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=148µm; 2=154µm 3=165µm, 30,1g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VTWasser 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm^2

mg DIOH / 5cm²					
Zeit [h]	1	2	3	**MW**	SD
3	0,24	0,36	0,39	**0,33**	0,08
6	0,34	0,42	0,45	**0,40**	0,06
24	1,46	1,52	1,56	**1,51**	0,05
30	1,75	1,80	1,84	**1,79**	0,05
48	2,33	2,38	2,43	**2,38**	0,05

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,22	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,98876	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

Schwarz Pharma AG

Analysenzertifikat

in vitro Freisetzung durch Mäusehaut

Präparat :	**SPM 907 TDS**
	SPM 7605
Ch.-B.:	20106045
TDS- Fläche :	5 cm²
Sollgehalt :	15%
Analysen-Nr:	20106043_6044_6045_6061_AA_MHP_01 + 02
Analysendatum :	09.07.2001
ABV vom :	analog OBU 0469.10

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=160µm; 2=168µm 3=148µm, 34,7g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
Ausgangsanalyse

Tabelle der kumulierten Freisetzung in mg / 5 cm²

mg DIOH / 5cm²					
Zeit [h]	1	2	3	**MW**	SD
3	0,09	0,09	0,09	**0,09**	0,00
6	0,35	0,36	0,43	**0,38**	0,05
24	1,16	1,16	1,21	**1,18**	0,03
30	1,36	1,35	1,39	**1,37**	0,02
48	1,83	1,77	1,83	**1,81**	0,04

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,12	mg
Regressionskoeffizient (m) =	0,04	mg/h
Korrelationskoeffizient (r) =	0,98181	

$$Q \approx t \qquad Q = t \cdot m + b$$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIII

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	**SPM 907 TDS**
	SPM 7605
Ch.-B.:	20106043
TDS- Fläche :	5 cm^2
Sollgehalt :	15%
Analysen-Nr:	20106043_6044_6045_6061_AA_MHP_01 + 02
Analysendatum :	09.07.2001
ABV vom :	analog OBU 0469.10

Bemerkungen: 8 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=174µm; 2=179µm 3=168µm, 31,7g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
Ausgangsanalyse

Tabelle der kumulierten Freisetzung in mg / 5 cm^2

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	**MW**	SD
3	0,07	0,27	0,08	**0,14**	0,11
6	0,38	0,76	0,37	**0,50**	0,22
24	1,59	2,45	1,47	**1,84**	0,54
30	1,98	2,94	1,82	**2,25**	0,61
48	3,00	4,10	2,63	**3,24**	0,77

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,07	mg
Regressionskoeffizient (m) =	0,07	mg/h
Korrelationskoeffizient (r) =	0,99521	

$Q \approx t$ $\quad Q = t \cdot m + b$

Q = Freisetzung in mg/5cm² t = Zeit in h (3h-48h)

Datum	Sachbearbeiter(in), PHA	Projektgruppenleiter, PGIV

Diffusion experiment with SPM 907 patches on silastic sheeting

Purpose of the study:

To investigate the influence of four formulations on the release rate of SPM 907 patches. The present study has been performed without skin in the cells in order to measure the initial release rate of active ingredient from the formulations through the used membrane. The four following experiments will be performed with skin from four different donors.

Patch:

Active ingredient: SPM 907
Batch numbers: 20012029, 20012036, 20106043 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Diffusion experiment:

Date: 7 to 10 Sept. 2001

Used cells:
diffusion cells with spiral groove (n=8); groove area: 0.552 cm^2.

Separator between acceptor phase and skin/patch:
Silicone sheeting (Silastic sheeting), implant grade elastomer non sterile, non-reinforced;
Manufacturer: Nagor limited, P.O. Box 21, Douglas, Island of Man
Cat. nr. NA 500-1, Thickness 0.125 mm, Lot nr. 11603/1
No special pretreatment, other than cleaning, applied.

Diameter of separator and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr.	Batch
1 & 2	20012029
3 & 4	20012036
5 & 6	20106043
7 & 8	20106061

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 32.0 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

Some sample from cell 5 was lost at 69 and 72 hours due to a tilted tube holder in the fraction collector. Use a higher volume for the corresponding fractionsfor calculations (see Volume fractions tab).

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,010 g/ml

Faktor zur Umrechnung auf cm²: 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes (g) full	fractions (ml)	8272 µg/ml	8272 µg/fraction	Fraction *F=1,812	Fraction Mittelwert	DiOH µg/ml	DiOH µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert	Diacetat µg/ml	Diacetat µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert
3	1	17,152	33,385	16,074					0,44	7,073	12,815		17,44	280,328	507,955	
	2	16,972	32,800	15,673					0,45	7,053	12,780	12,798	16,44	257,661	466,883	487,419
	3	17,146	33,037	15,735					0,42	6,609	11,975		18,30	287,955	521,774	
	4	16,884	32,889	15,848					0,73	11,569	20,963	16,469	22,20	351,828	637,512	579,643
	5	17,191	33,293	15,944					0,39	6,218	11,267					
	6	17,144	32,870	15,572					0,25	3,893	7,054	9,161				
	7	17,129	32,663	15,382	0,30	4,615	8,362		0,11	1,692	3,066					
	8	16,997	32,554	15,404	0,33	5,083	9,211	8,786	0,11	1,694	3,070	3,068				
6	1	16,790	33,002	16,053					0,34	5,458	9,890		14,49	232,609	421,488	
	2	17,018	32,890	15,716					0,48	7,544	13,670	11,780	14,54	228,517	414,072	417,780
	3	16,932	32,870	15,782					0,38	5,997	10,867		14,5	228,836	414,650	
	4	17,137	33,168	15,874					0,54	8,572	15,532	13,199	16,48	261,601	474,021	444,336
	5	17,140	33,322	16,023					1,02	16,344	29,615					
	6	17,215	33,036	15,666					0,86	13,473	24,412	27,014				
	7	16,946	32,586	15,487	0,49	7,59	13,750		0,15	2,323	4,209					
	8	17,071	32,807	15,582	0,44	6,86	12,423	13,087	0,12	1,870	3,388	3,799				
9	1	17,177	33,387	16,051					0,3	4,82	8,725		10,18	163,40	296,081	
	2	17,100	32,962	15,707					0,38	5,97	10,815	9,770	10,36	162,72	294,848	295,464
	3	17,125	33,070	15,789					0,27	4,26	7,724		11,23	177,31	321,280	
	4	17,160	33,197	15,880					0,32	5,08	9,208	8,466	12,62	200,40	363,130	342,205
	5	16,994	33,152	16,000					0,86	13,76	24,933					
	6	16,963	32,736	15,618					0,77	12,03	21,791	23,362				
	7	17,074	32,691	15,464	0,37	5,72	10,368		0,13	2,01	3,643					
	8	17,217	32,949	15,578	0,32	4,98	9,033	9,700	0,1	1,56	2,823	3,233				
12	1	17,202	33,391	16,030					0,27	4,33	7,843		7,65	122,63	222,209	
	2	16,912	32,768	15,701					0,27	4,24	7,681	7,762	7,74	121,52	220,199	221,204
	3	17,114	33,033	15,763					0,33	5,20	9,426		8,88	139,97	253,635	
	4	17,089	33,104	15,858					0,35	5,55	10,057	9,741	9,82	155,73	282,175	267,905
	5	17,143	33,302	16,001					0,72	11,52	20,875					
	6	17,146	32,922	15,621					0,63	9,84	17,833	19,354				
	7	17,192	32,846	15,501	0,25	3,88	7,022		0,1	1,55	2,809					
	8	17,224	32,937	15,559	0,23	3,58	6,484	6,753	0,08	1,24	2,255	2,532				

15	1	17,338	33,503	16,007					0,16	2,56	4,641		6,09	97,48	176,633	
	2	16,941	32,787	15,691					0,18	2,82	5,118	4,879	6,05	94,93	172,010	174,322
	3	17,152	33,082	15,774					0,24	3,79	6,860		7,40	116,73	211,508	
	4	17,031	33,043	15,855					0,18	2,85	5,171	6,016	8,26	130,96	237,304	224,406
	5	17,156	33,304	15,990					0,63	10,07	18,253					
	6	17,126	32,889	15,608					0,55	8,58	15,555	16,904				
	7	17,141	32,723	15,429	0,16	2,47	4,473		0,08	1,23	2,237					
	8	17,204	32,906	15,548	0,16	2,49	4,508	4,490	0,07	1,09	1,972	2,104				
18	1	17,058	33,216	16,000					0,17	2,72	4,929		5,01	80,16	145,246	
	2	17,180	32,996	15,661					0,13	2,04	3,689	4,309	5,00	78,30	141,888	143,567
	3	17,159	33,061	15,746					0,23	3,62	6,562		6,80	107,07	194,017	
	4	17,142	33,135	15,836					0,18	2,85	5,165	5,864	6,19	98,03	177,623	185,820
	5	17,253	33,387	15,976					0,53	8,47	15,343					
	6	17,180	32,932	15,598					0,48	7,49	13,566	14,454				
	7	17,130	32,740	15,457	0,12	1,85	3,361		0,06	0,93	1,680					
	8	17,201	32,906	15,551	0,13	2,02	3,663	3,512	0,06	0,93	1,691	1,686				
21	1	17,062	33,180	15,960					0,13	2,07	3,760		4,32	68,95	124,932	
	2	16,977	32,775	15,643					0,11	1,72	3,118	3,439	4,30	67,27	121,885	123,409
	3	16,944	32,827	15,727					0,19	2,99	5,415		5,22	82,10	148,759	
	4	17,145	33,102	15,801					0,21	3,32	6,012	5,714	5,81	91,80	166,344	157,551
	5	17,130	33,244	15,956					0,44	7,02	12,721					
	6	17,229	32,962	15,579					0,42	6,54	11,856	12,289				
	7	17,187	32,789	15,449	0,09	1,39	2,519		0,05	0,77	1,400					
	8	17,253	32,922	15,515	0,10	1,55	2,811	2,665	0,05	0,78	1,406	1,403				
24	1	17,048	33,153	15,947					0,11	1,75	3,179		3,76	59,96	108,650	
	2	17,157	32,956	15,644					0,14	2,19	3,969	3,574	3,71	58,04	105,168	106,909
	3	17,021	32,881	15,705					0,18	2,83	5,122		4,47	70,20	127,201	
	4	17,088	33,032	15,788					0,2	3,16	5,721	5,422	5,05	79,73	144,467	135,834
	5	17,192	33,301	15,951					0,37	5,90	10,694					
	6	17,149	32,839	15,536					0,37	5,75	10,416	10,555				
	7	17,099	32,662	15,410	0,07	1,08	1,955		0,04	0,62	1,117					
	8	17,042	32,683	15,488	0,08	1,24	2,245	2,100	0,03	0,46	0,842	0,979				

27	1	17,160	33,256	15,938					0,15	2,39	4,332		3,25	51,80	93,860		
	2	16,898	32,657	15,605					0,12	1,87	3,393	3,863	3,29	51,34	93,026	93,443	
	3	17,190	33,069	15,723					0,13	2,04	3,704		3,96	62,26	112,823		
	4	17,044	32,981	15,781					0,17	2,68	4,861	4,282	4,41	69,59	126,103	119,463	
	5	16,967	33,041	15,916					0,32	5,09	9,229						
	6	16,960	32,652	15,538					0,32	4,97	9,010	9,119					
	7	17,200	32,750	15,398	0,06	0,92	1,674		0,04	0,62	1,116						
	8	17,058	32,679	15,468	0,06	0,93	1,682	1,678	0,03	0,46	0,841	0,978					
30	1	17,166	33,255	15,931					0,08	1,27	2,309		2,97	47,32	85,736		
	2	17,179	32,950	15,616					0,09	1,41	2,547	2,428	2,91	45,44	82,344	84,040	
	3	17,301	33,134	15,678					0,15	2,35	4,261		3,46	54,25	98,292		
	4	17,049	32,984	15,779					0,16	2,52	4,575	4,418	3,91	61,70	111,791	105,042	
	5	17,158	33,243	15,927					0,27	4,30	7,792						
	6	17,106	32,814	15,554					0,26	4,04	7,328	7,560					
	7	17,285	32,852	15,414	0,05	0,77	1,397		0,03	0,46	0,838						
	8	17,129	32,736	15,454	0,05	0,77	1,400	1,398	0,02	0,31	0,560	0,699					
33	1	17,090	33,169	15,921					0,11	1,75	3,173		2,63	41,87	75,874		
	2	17,135	32,891	15,602					0,11	1,72	3,110	3,142	2,62	40,88	74,067	74,971	
	3	17,162	33,026	15,708					0,12	1,89	3,416		3,11	48,85	88,522		
	4	17,027	32,953	15,770					0,16	2,52	4,572	3,994	3,49	55,04	99,727	94,125	
	5	17,207	33,300	15,935					0,22	3,51	6,352						
	6	17,032	32,704	15,518					0,21	3,26	5,905	6,129					
	7	17,116	32,677	15,408	0,04	0,62	1,117		0,03	0,46	0,838						
	8	17,167	32,780	15,460	0,04	0,62	1,121	1,119	0,02	0,31	0,560	0,699					
36	1	17,015	33,086	15,913					0,1	1,59	2,884		2,02	32,15	58,247		
	2	17,323	33,093	15,615					0,09	1,41	2,547	2,715	2,10	32,79	59,420	58,833	
	3	17,024	32,893	15,713					0,13	2,04	3,701		2,41	37,87	68,619		
	4	17,131	33,044	15,757					0,14	2,21	3,997	3,849	2,74	43,17	78,232	73,425	
	5	17,142	33,219	15,919					0,2	3,18	5,769						
	6	17,166	32,865	15,545					0,18	2,80	5,070	5,420					
	7	16,871	32,428	15,404	0,04	0,62	1,117		0,03	0,46	0,837						
	8	16,963	32,568	15,452	0,04	0,62	1,120	1,118	0,02	0,31	0,560	0,699					

39	1	17,202	33,239	15,880					0,13	2,06	3,741		2,02	32,08	58,124		
	2	17,182	32,896	15,560					0,15	2,33	4,229	3,985	2,10	32,68	59,209	58,666	
	3	17,019	32,828	15,654					0,14	2,19	3,971		2,41	37,73	68,360		
	4	17,234	33,135	15,745					0,16	2,52	4,565	4,268	2,74	43,14	78,173	73,266	
	5	17,273	33,314	15,884					0,17	2,70	4,893						
	6	17,110	32,773	15,509					0,14	2,17	3,934	4,414					
	7	17,102	32,627	15,373	0,03	0,46	0,836		0,05	0,77	1,393						
	8	17,151	32,718	15,414	0,03	0,46	0,838	0,837	0,02	0,31	0,559	0,976					
42	1	16,781	32,820	15,882					0,12	1,91	3,453		1,81	28,75	52,088		
	2	17,124	32,853	15,575					0,12	1,87	3,387	3,420	1,93	30,06	54,468	53,278	
	3	16,957	32,794	15,682					0,14	2,20	3,978		2,14	33,56	60,809		
	4	17,049	32,937	15,732					0,15	2,36	4,276	4,127	2,46	38,70	70,127	65,468	
	5	17,281	33,334	15,896					0,15	2,38	4,320						
	6	17,168	32,840	15,518					0,12	1,86	3,374	3,847					
	7	17,056	32,563	15,355	0,03	0,46	0,835		0,02	0,31	0,556						
	8	17,056	32,637	15,428	0,03	0,46	0,839	0,837	0,02	0,31	0,559	0,558					
45	1	17,412	33,449	15,880					0,18	2,86	5,179		1,76	27,95	50,643		
	2	16,824	32,546	15,568					0,14	2,18	3,949	4,564	1,74	27,09	49,084	49,863	
	3	17,072	32,898	15,671					0,13	2,04	3,691		1,88	29,46	53,384		
	4	17,122	33,024	15,746					0,15	2,36	4,280	3,986	2,15	33,85	61,344	57,364	
	5	17,233	33,294	15,904					0,13	2,07	3,746						
	6	17,308	32,963	15,502					0,12	1,86	3,371	3,558					
	7	17,105	32,651	15,394	0,03	0,46	0,837		0,03	0,46	0,837						
	8	16,777	32,338	15,408	0,03	0,46	0,838	0,837	0,02	0,31	0,558	0,698					
48	1	17,169	33,192	15,866					0,12	1,90	3,450		1,62	25,70	46,573		
	2	17,140	32,865	15,571					0,11	1,71	3,104	3,277	1,57	24,45	44,297	45,435	
	3	17,055	32,874	15,664					0,12	1,88	3,406		1,70	26,63	48,251		
	4	17,138	33,008	15,714					0,14	2,20	3,986	3,696	1,96	30,80	55,810	52,031	
	5	17,157	33,186	15,872					0,13	2,06	3,739						
	6	17,224	32,863	15,486					0,10	1,55	2,806	3,272					
	7	17,019	32,519	15,348	0,02	0,31	0,556		0,02	0,31	0,556						
	8	17,210	32,778	15,415	0,02	0,31	0,559	0,557	0,02	0,31	0,559	0,557					

51	1	16,998	33,013	15,858					0,09	1,43	2,586		1,26	19,98	36,206	
	2	16,957	32,667	15,556					0,09	1,40	2,537	2,561	1,57	24,42	44,254	40,230
	3	17,200	33,025	15,670					0,07	1,10	1,988		1,62	25,39	45,998	
	4	16,882	32,762	15,724					0,10	1,57	2,849	2,418	1,79	28,15	51,002	48,500
	5	17,035	33,097	15,905					0,13	2,07	3,746					
	6	17,037	32,688	15,498					0,09	1,39	2,527	3,137				
	7	17,032	32,544	15,360	0,02	0,31	0,557		0,02	0,31	0,557					
	8	16,933	32,466	15,381	0,02	0,31	0,557	0,557	0,01	0,15	0,279	0,418				
54	1	17,124	33,127	15,846					0,07	1,11	2,010		1,07	16,96	30,723	
	2	17,131	32,852	15,567					0,08	1,25	2,257	2,133	1,39	21,64	39,208	34,966
	3	17,145	32,950	15,650					0,08	1,25	2,269		1,42	22,22	40,268	
	4	16,555	32,424	15,713					0,09	1,41	2,563	2,416	1,68	26,40	47,834	44,051
	5	17,062	33,093	15,874					0,11	1,75	3,164					
	6	17,071	32,731	15,506					0,09	1,40	2,529	2,846				
	7	17,085	32,588	15,351	0,02	0,31	0,556		0,02	0,31	0,556					
	8	17,135	32,700	15,412	0,02	0,31	0,559	0,557	0,02	0,31	0,559	0,557				
57	1	16,921	32,921	15,843					0,06	0,95	1,722		0,89	14,10	25,550	
	2	17,121	32,799	15,524					0,07	1,09	1,969	1,846	1,20	18,63	33,756	29,653
	3	17,100	32,890	15,635					0,08	1,25	2,266		1,29	20,17	36,547	
	4	17,235	33,100	15,709					0,09	1,41	2,562	2,414	1,58	24,82	44,976	40,761
	5	17,011	33,051	15,883					0,10	1,59	2,878					
	6	17,281	32,916	15,482					0,08	1,24	2,244	2,561				
	7	17,040	32,552	15,360	0,02	0,31	0,557		0,02	0,31	0,557					
	8	16,959	32,493	15,382	0,02	0,31	0,557	0,557	0,01	0,15	0,279	0,418				
60	1	17,058	33,061	15,846					0,06	0,95	1,723		0,78	12,36	22,396	
	2	16,788	32,464	15,522					0,06	0,93	1,688	1,705	1,01	15,68	28,408	25,402
	3	17,092	32,898	15,651					0,07	1,10	1,985		1,12	17,53	31,763	
	4	17,035	32,888	15,698					0,09	1,41	2,560	2,273	1,53	24,02	43,519	37,641
	5	17,144	33,161	15,860					0,09	1,43	2,586					
	6	17,147	32,787	15,487					0,07	1,08	1,964	2,275				
	7	16,978	32,488	15,358	0,02	0,31	0,557		0,02	0,31	0,557					
	8	17,109	32,657	15,396	0,02	0,31	0,558	0,557	0,01	0,15	0,279	0,418				

63	1	17,216	33,211	15,838					0,03	0,48	0,861		0,87	13,78	24,968		
	2	16,955	32,651	15,542					0,03	0,47	0,845	0,853	1,14	17,72	32,105	28,537	
	3	17,047	32,856	15,654					0,03	0,47	0,851		1,11	17,38	31,485		
	4	16,515	32,367	15,697					0,05	0,78	1,422	1,137	1,52	23,86	43,232	37,359	
	5	17,071	33,073	15,845					0,08	1,27	2,297						
	6	14,708	30,341	15,480					0,06	0,93	1,683	1,990					
	7	17,010	32,519	15,357	0,02	0,31	0,557		0,01	0,15	0,278						
	8	17,150	32,720	15,417	0,02	0,31	0,559	0,558	0,01	0,15	0,279	0,279					
66	1	17,211	33,181	15,813					0,03	0,47	0,860		0,77	12,18	22,064		
	2	17,353	33,060	15,553					0,06	0,93	1,691	1,275	1,62	25,20	45,655	33,859	
	3	17,164	32,961	15,642					0,04	0,63	1,134		0,97	15,17	27,493		
	4	16,873	32,692	15,664					0,07	1,10	1,987	1,560	2,35	36,81	66,700	47,097	
	5	17,131	33,153	15,865					0,08	1,27	2,300						
	6	17,051	32,650	15,446					0,06	0,93	1,679	1,990					
	7	17,083	32,585	15,350	0,02	0,31	0,556		0,01	0,15	0,278						
	8	17,042	32,588	15,394	0,01	0,15	0,279	0,418	0,01	0,15	0,279	0,279					
69	1	17,029	33,015	15,829					0,04	0,63	1,147		0,66	10,45	18,931		
	2	17,192	32,894	15,548					0,06	0,93	1,690	1,419	1,22	18,97	34,371	26,651	
	3	17,010	32,807	15,642					0,04	0,63	1,134		0,82	12,83	23,242		
	4	17,262	33,100	15,683					0,08	1,25	2,273	1,704	2,01	31,52	57,118	40,180	
	5	17,146	29,984	12,712					0,07	1,11	2,017						
	6	17,184	32,778	15,441					0,06	0,93	1,679	1,848					
	7	17,162	32,657	15,343	0,02	0,31	0,556		0,01	0,15	0,278						
	8	16,977	32,471	15,342	0,01	0,15	0,278	0,417	0,01	0,15	0,278	0,278					
72	1	16,788	32,776	15,831					0,03	0,47	0,861		0,58	9,18	16,638		
	2	16,986	32,671	15,531					0,06	0,93	1,689	1,275	1,30	20,19	36,585	26,612	
	3	17,113	32,910	15,642					0,03	0,47	0,850		0,68	10,64	19,274		
	4	17,203	33,058	15,700					0,05	0,78	1,422	1,136	1,76	27,63	50,068	34,671	
	5	17,137	32,175	14,891					0,07	1,11	2,017						
	6	16,830	32,396	15,413					0,06	0,92	1,676	1,846					
	7	17,051	32,574	15,371	0,01	0,15	0,279		0,01	0,15	0,279						
	8	17,224	32,743	15,367	0,01	0,15	0,278	0,278	0,01	0,15	0,278	0,278					

Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF002

Purpose of the study:

To investigate the release rate of SPM 907 from four different formulations of patches. The present experiment is the first in a series of four in which the flux from the four formulations through skin from four different donors is measured. The fluxes through the supportive membrane have been investigated in a previous experiment.

Patch:

Active ingredient: SPM 907
Batch numbers: 20012029, 20012036, 20106043 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Skin donor:

Birth date: 06.12.1983
Sex: female
Skin from: breast
Thickness of dermatomised skin: approximately 290 µm, skin in cell 8 was app. 350 µm.

Diffusion experiment:

Date: 10 to 13 october 2001

Used cells:
diffusion cells with spiral groove (n=8); groove area: 0.552 cm^2.

Separator between acceptor phase and skin/patch:
Silicone sheeting (Silastic sheeting), implant grade elastomer non sterile, non-reinforced;
Manufacturer: Nagor limited, P.O. Box 21, Douglas, Island of Man
Cat. nr. NA 500-1, Thickness 0.125 mm, Lot nr. 11603/1
No special pretreatment, other than cleaning, applied.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr.	Batch
1 & 2	20012029
3 & 4	20012036
5 & 6	20106043
7 & 8	20106061

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 32,0 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

No special observations.

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,008 g/ml

Faktor zur Umrechnung auf cm³= 1,812

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes (g) full	volume fraction	8272 µg/ml	8272 µg/fraction	Fraction *F=1.812	Fraction Mittelwert	DiOH µg/ml	DiOH µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert	Diacetat µg/ml	Diacetat µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert
3	1	17,063	33,268	16,075					0,02	0,322	0,583		0	0	0,000	
	2	17,231	33,311	15,951					0,02	0,319	0,578	0,580	0	0	0,000	0,000
	3	17,137	33,225	15,959					0,01	0,160	0,289		0	0	0,000	
	4	17,069	33,212	16,014					0,01	0,160	0,290	0,290	0	0	0,000	0,000
	5	17,158	33,501	16,212					0,01	0,162	0,294					
	6	17,154	32,990	15,709					0,01	0,157	0,285	0,289				
	7	17,265	32,997	15,606	0	0,000			0,01	0,156	0,283					
	8	17,037	32,889	15,725	0	0,000			0,01	0,157	0,285	0,284				
6	1	16,973	33,218	16,115					0,00	0	0,000		0	0,000	0,000	
	2	16,968	33,123	16,026					0,00	0	0,000		0	0,000	0,000	0,000
	3	16,925	33,047	15,993					0,00	0	0,000		0	0,000	0,000	
	4	17,253	33,391	16,009					0,00	0	0,000		0,01	0,160	0,290	0,145
	5	17,140	33,511	16,240					0,00	0	0,000					
	6	17,272	33,188	15,789					0,00	0	0,000					
	7	17,198	32,921	15,597	0	0,000			0,00	0	0,000					
	8	17,144	33,052	15,781	0	0,000			0,00	0	0,000					
9	1	17,039	33,261	16,092					0,00	0	0,000		0	0,000	0,000	
	2	17,064	33,200	16,007					0,00	0	0,000		0,01	0,160	0,290	0,145
	3	17,219	33,343	15,995					0,00	0	0,000		0,05	0,800	1,449	
	4	17,036	33,172	16,007					0,00	0	0,000		0,01	0,160	0,290	0,870
	5	17,174	33,553	16,248					0,00	0	0,000					
	6	17,078	32,965	15,760					0,00	0	0,000					
	7	17,062	32,796	15,608	0	0,000			0,00	0	0,000					
	8	17,156	33,061	15,778	0	0,000			0,00	0	0,000					
12	1	17,272	33,469	16,067					0,00	0	0,000			0,000	0,000	
	2	17,232	33,364	16,003					0,00	0	0,000		0,01	0,160	0,290	0,145
	3	17,232	33,359	15,998					0,00	0	0,000		0,06	0,960	1,739	
	4	17,047	33,169	15,993					0,00	0	0,000		0,01	0,160	0,290	1,015
	5	17,264	33,626	16,231					0,00	0	0,000					
	6	17,188	33,089	15,774					0,00	0	0,000					
	7	17,069	32,813	15,618	0	0,000			0,00	0	0,000					
	8	17,162	33,066	15,777	0	0,000			0,00	0	0,000					

15	1	17,133	33,356	16,093					0,01	0,161	0,292			0,000	0,000				
	2	17,221	33,339	15,989					0,01	0,160	0,290	0,291	0,03	0,480	0,869	0,435			
	3	17,159	33,254	15,966					0,01	0,160	0,289		0,08	1,277	2,314				
	4	17,080	33,187	15,978					0,00	0,000	0,000	0,145	0,01	0,160	0,290	1,302			
	5	17,144	33,513	16,238					0,01	0,162	0,294								
	6	16,950	32,833	15,756					0,01	0,158	0,285	0,290							
	7	17,113	32,849	15,610	0	0,000			0,01	0,156	0,283								
	8	16,931	32,855	15,797	0	0,000			0,00	0,000	0,000	0,141							
18	1	17,087	33,288	16,071					0,01	0,161	0,291		0	0,000	0,000				
	2	16,704	32,823	15,990					0,01	0,160	0,290	0,290	0,03	0,480	0,869	0,435			
	3	16,880	33,009	16,000					0,00	0,000	0,000		0,08	1,280	2,319				
	4	17,119	33,251	16,003					0,00	0,000	0,000	0,000	0,01	0,160	0,290	1,305			
	5	16,977	33,332	16,224					0,00	0,000	0,000								
	6	17,091	32,968	15,750					0,01	0,157	0,285	0,143							
	7	16,910	32,651	15,615	0	0,000			0,01	0,156	0,283								
	8	16,902	32,819	15,790	0	0,000			0,02	0,316	0,572	0,428							
21	1	16,554	32,677	15,994					0,00	0,000	0,000		0	0,000	0,000				
	2	17,028	33,082	15,925					0,00	0,000	0,000	0,000	0,04	0,637	1,154	0,577			
	3	17,191	33,238	15,919					0,00	0,000	0,000		0,07	1,114	2,019				
	4	17,182	33,231	15,921					0,00	0,000	0,000	0,000	0,02	0,318	0,577	1,298			
	5	17,090	33,395	16,174					0,01	0,162	0,293								
	6	17,098	32,920	15,695					0,00	0,000	0,000	0,147							
	7	17,147	32,805	15,533	0	0,000			0,01	0,155	0,281								
	8	17,063	32,897	15,707	0	0,000			0,00	0,000	0,000	0,141							
24	1	16,779	32,906	15,998					0,00	0,000	0,000		0,01	0,160	0,290				
	2	17,282	33,307	15,897					0,01	0,159	0,288	0,144	0,05	0,795	1,440	0,865			
	3	17,038	33,072	15,906					0,01	0,159	0,288		0,10	1,591	2,882				
	4	17,057	33,100	15,915					0,01	0,159	0,288	0,288	0,04	0,637	1,153	2,018			
	5	16,955	33,249	16,164					0,01	0,162	0,293								
	6	17,161	32,951	15,664					0,00	0,000	0,000	0,146							
	7	17,089	32,759	15,545	0	0,000			0,01	0,155	0,282								
	8	17,303	33,151	15,721	0	0,000			0,01	0,157	0,285	0,283							

27	1	17,156	33,272	15,987					0,01	0,160	0,290		0,01	0,160	0,290			
	2	17,177	33,213	15,908					0,00	0,000	0,000	0,145	0,05	0,795	1,441	0,865		
	3	17,322	33,345	15,895					0,01	0,159	0,288		0,09	1,431	2,592			
	4	17,155	33,189	15,906					0,01	0,159	0,288	0,288	0,05	0,795	1,441	2,017		
	5	16,824	33,108	16,154					0,00	0,000	0,000							
	6	17,098	32,893	15,669					0,00	0,000	0,000	0,000						
	7	17,086	32,719	15,508	0	0,000			0,01	0,155	0,281							
	8	17,046	32,877	15,704	0	0,000			0,00	0,000	0,000	0,141						
30	1	17,227	33,305	15,949					0,01	0,159	0,289		0,02	0,319	0,578			
	2	17,126	33,126	15,872					0,00	0,000	0,000	0,145	0,06	0,952	1,726	1,152		
	3	17,123	33,142	15,891					0,00	0,000	0,000		0,07	1,112	2,016			
	4	17,102	33,119	15,889					0,01	0,159	0,288	0,144	0,06	0,953	1,727	1,872		
	5	17,133	33,400	16,137					0,01	0,161	0,292							
	6	17,200	32,962	15,636					0,01	0,156	0,283	0,288						
	7	17,103	32,765	15,537	0	0,000			0,01	0,155	0,282							
	8	17,008	32,812	15,677	0	0,000			0,01	0,157	0,284	0,283						
33	1	17,009	33,103	15,965					0,01	0,160	0,289		0,03	0,479	0,868			
	2	17,187	33,175	15,860					0,01	0,159	0,287	0,288	0,06	0,952	1,724	1,296		
	3	17,167	33,152	15,857					0,01	0,159	0,287		0,08	1,269	2,299			
	4	17,058	33,041	15,855					0,02	0,317	0,575	0,431	0,09	1,427	2,586	2,442		
	5	16,977	33,221	16,114					0,01	0,161	0,292							
	6	17,230	32,996	15,640					0,01	0,156	0,283	0,288						
	7	17,107	32,737	15,505	0	0,000			0,01	0,155	0,281							
	8	17,179	32,994	15,688	0	0,000			0,00	0,000	0,000	0,140						
36	1	17,411	33,461	15,922					0,01	0,159	0,288		0,03	0,478	0,865			
	2	17,053	33,025	15,844					0,01	0,158	0,287	0,288	0,06	0,951	1,723	1,294		
	3	16,895	32,897	15,874					0,03	0,476	0,863		0,08	1,270	2,301			
	4	17,271	33,262	15,863					0,01	0,159	0,287	0,575	0,10	1,586	2,874	2,588		
	5	17,231	33,482	16,121					0,01	0,161	0,292							
	6	17,189	32,931	15,616					0,01	0,156	0,283	0,288						
	7	17,143	32,777	15,509	0	0,000			0,01	0,155	0,281							
	8	16,937	32,718	15,655	0	0,000			0,01	0,157	0,284	0,282						

39	1	16,980	32,874	15,767					0,02	0,315	0,571		0,04	0,631	1,143		
	2	16,918	32,706	15,662					0,02	0,313	0,568	0,569	0,07	1,096	1,987	1,565	
	3	16,981	32,769	15,662					0,02	0,313	0,568		0,08	1,253	2,270		
	4	16,992	32,801	15,682					0,03	0,470	0,852	0,710	0,1	1,568	2,842	2,556	
	5	16,962	33,025	15,934					0,01	0,159	0,289						
	6	17,245	32,812	15,442					0,01	0,154	0,280	0,284					
	7	17,178	32,609	15,307	0	0,000			0,01	0,153	0,277						
	8	17,178	32,765	15,462	0	0,000			0,01	0,155	0,280	0,279					
42	1	17,126	33,013	15,760					0,01	0,158	0,286		0,04	0,630	1,142		
	2	16,919	32,716	15,671					0,10	1,567	2,840	1,563	0,07	1,097	1,988	1,565	
	3	17,302	33,113	15,684					0,02	0,314	0,568		0,10	1,568	2,842		
	4	17,237	33,036	15,673					0,04	0,627	1,136	0,852	0,15	2,351	4,260	3,551	
	5	17,248	33,294	15,918					0,01	0,159	0,288						
	6	14,706	30,240	15,410					0,01	0,154	0,279	0,284					
	7	17,169	32,612	15,319	0	0,000			0,01	0,153	0,278						
	8	17,208	32,824	15,491	0	0,000			0,01	0,155	0,281	0,279					
45	1	16,976	32,857	15,754					0,02	0,315	0,571		0,05	0,788	1,427		
	2	16,941	32,733	15,666					0,01	0,157	0,284	0,427	0,08	1,253	2,271	1,849	
	3	17,075	32,886	15,684					0,02	0,314	0,568		0,12	1,882	3,410		
	4	16,946	32,755	15,682					0,03	0,470	0,852	0,710	0,16	2,509	4,547	3,979	
	5	17,065	33,125	15,931					0,01	0,159	0,289						
	6	17,252	32,829	15,452					0,01	0,155	0,280	0,284					
	7	16,465	31,911	15,322	0	0,000			0,01	0,153	0,278						
	8	17,074	32,688	15,489	0	0,000			0,01	0,155	0,281	0,279					
48	1	17,011	32,888	15,750					0	0,000	0,000		0,05	0,787	1,427		
	2	17,364	33,150	15,660					0,01	0,157	0,284	0,142	0,08	1,253	2,270	1,848	
	3	17,181	32,987	15,679					0,01	0,157	0,284		0,10	1,568	2,841		
	4	17,084	32,889	15,678					0,03	0,470	0,852	0,568	0,17	2,665	4,830	3,835	
	5	17,023	33,075	15,923					0,01	0,159	0,289						
	6	17,106	32,647	15,417					0,01	0,154	0,279	0,284					
	7	17,072	32,525	15,329	0	0,000			0,01	0,153	0,278						
	8	17,186	32,806	15,495	0	0,000			0,01	0,155	0,281	0,279					

51	1	17,008	32,899	15,764					0,02	0,315	0,571		0,08	1,261	2,285		
	2	17,008	32,784	15,650					0,02	0,313	0,567	0,569	0,11	1,721	3,119	2,702	
	3	17,053	32,858	15,678					0,02	0,314	0,568		0,17	2,665	4,830		
	4	17,052	32,846	15,668					0,04	0,627	1,136	0,852	0,23	3,604	6,530	5,680	
	5	17,074	33,113	15,911					0,01	0,159	0,288						
	6	17,090	32,645	15,430					0,01	0,154	0,280	0,284					
	7	16,921	32,368	15,323	0	0,000			0,01	0,153	0,278						
	8	17,188	32,801	15,488	0	0,000			0,01	0,155	0,281	0,279					
54	1	17,024	32,887	15,736					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,143	32,909	15,640					0,01	0,156	0,283	0,427	0,10	1,564	2,834	2,558	
	3	17,206	32,999	15,667					0,02	0,313	0,568		0,17	2,663	4,826		
	4	17,112	32,902	15,664					0,05	0,783	1,419	0,993	0,25	3,916	7,096	5,961	
	5	17,024	33,057	15,905					0,01	0,159	0,288						
	6	17,029	32,589	15,435					0,01	0,154	0,280	0,284					
	7	16,997	32,427	15,306	0	0,000			0,01	0,153	0,277						
	8	16,884	32,487	15,478	0	0,000			0,01	0,155	0,280	0,279					
57	1	17,215	33,077	15,735					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,179	32,949	15,644					0,02	0,313	0,567	0,569	0,10	1,564	2,835	2,558	
	3	17,150	32,917	15,641					0,03	0,469	0,850		0,16	2,503	4,535		
	4	17,161	32,944	15,657					0,05	0,783	1,418	1,134	0,26	4,071	7,376	5,955	
	5	17,340	33,386	15,918					0,01	0,159	0,288						
	6	17,121	32,634	15,389					0,01	0,154	0,279	0,284					
	7	17,160	32,589	15,305	0	0,000			0,01	0,153	0,277						
	8	17,061	32,656	15,470	0	0,000			0,01	0,155	0,280	0,279					
60	1	17,166	33,031	15,738					0,02	0,315	0,570		0,08	1,259	2,281		
	2	17,098	32,868	15,644					0,02	0,313	0,567	0,569	0,16	2,503	4,535	3,408	
	3	16,869	32,654	15,659					0,03	0,470	0,851		0,18	2,819	5,107		
	4	17,014	32,800	15,660					0,05	0,783	1,419	1,135	0,26	4,072	7,378	6,242	
	5	17,138	33,174	15,908					0,01	0,159	0,288						
	6	17,178	32,701	15,399					0,01	0,154	0,279	0,284					
	7	16,970	32,401	15,307	0	0,000			0,01	0,153	0,277						
	8	17,166	32,725	15,434	0	0,000			0,01	0,154	0,280	0,279					

63	1	17,194	33,066	15,745					0,02	0,315	0,571		0,08	1,260	2,282		
	2	16,957	32,724	15,641					0,02	0,313	0,567	0,569	0,16	2,503	4,535	3,408	
	3	17,042	32,829	15,661					0,03	0,470	0,851		0,19	2,976	5,392		
	4	17,123	32,896	15,647					0,05	0,782	1,418	1,134	0,26	4,068	7,371	6,382	
	5	17,156	33,179	15,895					0,01	0,159	0,288						
	6	17,022	32,563	15,417					0,01	0,154	0,279	0,284					
	7	17,128	32,542	15,291	0	0,000			0,02	0,306	0,554						
	8	17,162	32,764	15,477	0	0,000			0,01	0,155	0,280	0,417					
66	1	16,513	32,343	15,703					0,02	0,314	0,569		0,08	1,256	2,276		
	2	16,996	32,752	15,630					0,02	0,313	0,566	0,568	0,15	2,344	4,248	3,262	
	3	17,050	32,829	15,653					0,03	0,470	0,851		0,19	2,974	5,389		
	4	16,604	32,400	15,670					0,04	0,627	1,136	0,993	0,26	4,074	7,382	6,386	
	5	17,202	33,230	15,900					0,01	0,159	0,288						
	6	17,275	32,800	15,401					0,01	0,154	0,279	0,284					
	7	17,185	32,630	15,321	0	0,000			0,01	0,153	0,278						
	8	17,186	32,776	15,465	0	0,000			0,01	0,155	0,280	0,279					
69	1	17,063	32,920	15,730					0,02	0,315	0,570		0,08	1,258	2,280		
	2	17,180	32,936	15,630					0,02	0,313	0,566	0,568	0,15	2,344	4,248	3,264	
	3	17,137	32,926	15,663					0,02	0,313	0,568		0,19	2,976	5,392		
	4	17,093	32,871	15,652					0,04	0,626	1,134	0,851	0,24	3,756	6,807	6,099	
	5	17,149	33,192	15,915					0,01	0,159	0,288						
	6	17,113	32,616	15,379					0,01	0,154	0,279	0,284					
	7	17,148	32,569	15,298	0	0,000			0,01	0,153	0,277						
	8	17,045	32,631	15,461	0	0,000			0,01	0,155	0,280	0,279					
72	1	17,201	33,058	15,730					0,02	0,315	0,570		0,08	1,258	2,280		
	2	17,072	32,832	15,634					0,02	0,313	0,567	0,568	0,14	2,189	3,966	3,123	
	3	17,053	32,826	15,647					0,02	0,313	0,567		0,20	3,129	5,670		
	4	17,204	32,981	15,651					0,04	0,626	1,134	0,851	0,26	4,069	7,373	6,522	
	5	16,992	33,009	15,889					0,01	0,159	0,288						
	6	17,046	32,564	15,394					0,01	0,154	0,279	0,283					
	7	17,144	32,549	15,282	0	0,000			0,01	0,153	0,277						
	8	17,032	32,628	15,471	0	0,000			0,01	0,155	0,280	0,279					

Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20003028
Sollgehalt :	4,0 mg	TDS- Fläche :	5 cm²
Analysen-Nr:	IN168A-B	Analysendatum :	28.03.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 9 Wochen lebend, 4 Wochen TK-Schrank; SKH-1♂
1=170 µm; 2=175 µm; 3=148 µm, 33,3g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C
;

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	MW	SD	MW
3	1,15	0,81	2,25	**1,40**	0,76	0,31
6	2,15	1,95	3,76	**2,62**	0,99	0,54
24	4,13	4,78	5,19	**4,70**	0,54	0,99
30	4,30	5,19	5,23	**4,91**	0,53	1,02
48	4,42	5,40	5,25	**5,02**	0,53	1,03

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 6,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	1,99	mg
Regressionskoeffizient (m) =	0,08	mg/h
Korrelationskoeffizient (r) =	0,88839	

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	MW	SD
3	0,26	0,20	0,32	**0,26**	0,06
6	0,47	0,39	0,52	**0,46**	0,07
24	1,07	1,05	0,93	**1,02**	0,07
30	1,13	1,10	0,96	**1,06**	0,09
48	1,19	1,15	0,98	**1,10**	0,11

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,35	mg
Regressionskoeffizient (m) =	0,02	mg/h
Korrelationskoeffizient (r) =	0,90552	

$Q \approx t$ $Q = t \cdot m + b$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20004038
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IN189 A,B	Analysendatum :	17.04.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 7 Wochen lebend, 2 Wochen TK-Schrank; SKH-1♂
1=159 µm; 2=165 µm; 3=146 µm, 31,9 g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	**MW**	SD	**MW**
3	0,14	0,15	0,20	**0,16**	0,03	0,04
6	1,21	1,17	1,28	**1,22**	0,06	0,22
24	2,27	2,17	2,35	**2,27**	0,09	0,41
30	2,48	2,37	2,54	**2,46**	0,09	0,43
48	2,75	2,63	2,75	**2,71**	0,07	0,46

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 6,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,62	mg
Regressionskoeffizient (m) =	0,05	mg/h
Korrelationskoeffizient (r) =	0,89901	

	mg DIOH / 5cm²				
Zeit [h]	1	2	3	**MW**	SD
3	0,07	0,07	0,08	**0,07**	0,01
6	0,38	0,39	0,37	**0,38**	0,01
24	0,71	0,72	0,68	**0,71**	0,02
30	0,77	0,77	0,72	**0,75**	0,03
48	0,83	0,83	0,77	**0,81**	0,03

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,21	mg
Regressionskoeffizient (m) =	0,02	mg/h
Korrelationskoeffizient (r) =	0,89243	

$Q = t$ $Q = t \cdot m + b$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Schwarz Pharma AG

Analysenzertifikat
in vitro Freisetzung durch Mäusehaut

Präparat :	INZ-TDS **SPM8302**	Ch.-B.:	20004039
Sollgehalt :		TDS- Fläche :	5 cm²
Analysen-Nr:	IN189 A,B	Analysendatum :	17.04.2000
ABV vom :	analog OBU 0469.100		

Bemerkungen: 7 Wochen lebend, 2 Wochen TK-Schrank; SKH-1♂
1=180 µm; 2=165 µm; 3=143 µm, 34,0 g
Die Proben wurden nicht aufkonzentriert und nicht filtriert
HPLC: 4VT Acetonitril / 6VT 0,1% TFA; Spherisorb 5CN 25cm; 35°C

Tabelle der kumulierten Freisetzung in mg / 5 cm²

	mg Diacetat / 5cm²					mg Monoacetat/5cm²**
Zeit [h]	1	2	3	**MW**	SD	**MW**
3	0,11	0,25	0,59	**0,32**	0,25	0,09
6	0,90	1,04	1,17	**1,03**	0,13	0,22
24	1,71	1,82	1,74	**1,76**	0,05	0,37
30	1,84	1,92	1,78	**1,85**	0,07	0,38
48	1,97	1,99	1,81	**1,92**	0,10	0,39

**Da für Monoacetat keine Standardsubstanz vorliegt, wurde der auftretende Peak bei RT 6,8 ohne Berücksichtigung des MG in Diacetat umgerechnet.
MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,65	mg
Regressionskoeffizient (m) =	0,03	mg/h
Korrelationskoeffizient (r) =	0,87148	

	mg DfOH / 5cm²				
Zeit [h]	1	2	3	**MW**	SD
3	0,06	0,08	0,13	**0,09**	0,04
6	0,32	0,33	0,34	**0,33**	0,01
24	0,60	0,58	0,55	**0,58**	0,02
30	0,64	0,60	0,57	**0,60**	0,03
48	0,68	0,63	0,58	**0,63**	0,05

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	0,20	mg
Regressionskoeffizient (m) =	0,01	mg/h
Korrelationskoeffizient (r) =	0,87353	

$$\mathbf{Q \approx t} \qquad \mathbf{Q = t \cdot m + b}$$

Q = Freisetzung in µg/5cm² t = Zeit in h (3h-48h)

Datum Sachbearbeiter(in), PHA Projektgruppenleiter, PGIV

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Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF003

Purpose of the study:

To investigate the release rate of SPM 907 from four different formulations of patches. The present experiment is the second in a series of four in which the flux from the four formulations through skin from four different donors is measured. Because of low flux values in the first experiment in this series, the silastic sheeting supportive membrane has been replaced with dialysis membrane.

Patch:

Active ingredient: SPM 907
Batch numbers: 20012029, 20012036 and 20106061
Patch area: (variable)
Active ingredient content: app. 15% m/m

Skin donor:

Birth date: 1969
Sex: female
Skin from: abdomen (belly)
Thickness of dermatomised skin: approximately 240 µm

Diffusion experiment:

Date: 15 to 18 november 2001

Used cells:
diffusion cells with spiral groove (n=6); groove area: 0.552 cm^2.

Separator between acceptor phase and skin/patch:
Diachema dialysis membrane, type 10.14, supplied by Dianorm, München, Germany.
Manufactured from neutral cellulose, molar weight cut-off: 5000, thickness (dry): 25 µm.
Pretreated according to the manufacturer's recommendations.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr.	Batch
1 & 2	20106061
3 & 4	20012029
5 & 6	20012036

Acceptor phase: PBS pH=6.2
Measured temperature waterbath: 31,9 °C
Flux of acceptor phase: 5 ml/hour
Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

1.) The total area of good quality skin on the delivered pieces allowed the punch-out of no more than six disks for use in the experiment. Therefore, only three of the four batches were tested.
2.) The skin disk in cell 1 contained a thinner area on one side.
3.) The skin disk in cell 6 was thinner on the whole area.
4.) The skin disks in cells 2, 3, 4 and 6 showed spots from the blue marker used to mark unusable areas on the skin pieces. Traces of the blue dye might be found in the corresponding diffusion samples.

Mass and volume data on the collected fractions

measured density of the used acceptor phase: 1,007 g/ml | Faktor zur Umrechnung auf cm³= **1,812**

Flux time (hours)	cell nr.	mass tubes (g) empty	mass tubes (g) full	volume fractions (ml)	8272 µg/ml	8272 µg/fraction	Fraction *F=1.812	Fraction Mittelwert	DiOH µg/ml	DiOH µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert	Diacetat µg/ml	Diacetat µg/fraction	FractionxF µg/cm²	FractionxF Mittelwert	
3	1	16,976	33,097	16,005	0,01	0,160	0,290005		0,03	0,480	0,870						
	2	17,155	32,862	15,594	0	0,000	0,000	0,145	0,02	0,312	0,565	0,718					
	3	16,962	32,718	15,642					0,04	0,626	1,134		0,56	8,760	15,873		
	4	16,966	32,573	15,494					0,02	0,310	0,562	0,848	0,02	0,310	0,562	8,217	3
	5	17,028	32,635	15,494					0,02	0,310	0,562		0,02	0,310	0,562		
	6	16,968	32,350	15,271					0,06	0,916	1,660	1,111	0,38	5,803	10,515	5,538	
6	1	17,156	33,289	16,017	0,01	0,160	0,290		0,04	0,641	1,161						
	2	17,179	32,907	15,615	0	0,000	0,000	0,145	0,02	0,312	0,566	0,863					
	3	17,281	33,008	15,614					0,09	1,405	2,546		0,61	9,524	17,258		
	4	17,157	32,757	15,487					0,02	0,310	0,561	1,554	0,01	0,155	0,281	8,769	6
	5	17,113	32,717	15,491					0,09	1,394	2,526		0,05	0,775	1,404		
	6	17,171	32,548	15,266					0,09	1,374	2,490	2,508	0,39	5,954	10,788	6,096	
9	1	16,873	33,002	16,013	0,01	0,160	0,290		0,06	0,961	1,741						
	2	17,271	32,988	15,604	0	0,000	0,000	0,145	0,03	0,468	0,848	1,295					
	3	17,027	32,743	15,603					0,1	1,560	2,827		0,57	8,893	16,115		
	4	17,229	32,838	15,496					0,06	0,930	1,685	2,256	0,02	0,310	0,562	8,338	9
	5	16,820	32,426	15,493					0,14	2,169	3,930		0,09	1,394	2,527		
	6	17,023	32,434	15,300					0,12	1,836	3,327	3,629	0,40	6,120	11,089	6,808	
12	1	17,111	33,253	16,026	0,02	0,321	0,581		0,07	1,122	2,033						
	2	17,046	32,781	15,621	0,01	0,156	0,283	0,432	0,04	0,625	1,132	1,582					
	3	17,145	32,896	15,637					0,12	1,876	3,400		0,57	8,913	16,151		
	4	16,727	32,342	15,502					0,09	1,395	2,528	2,964	0,05	0,775	1,405	8,778	12
	5	17,276	32,908	15,519					0,19	2,949	5,343		0,13	2,017	3,656		
	6	16,950	32,391	15,330					0,13	1,993	3,611	4,477	0,41	6,285	11,389	7,522	
15	1	17,230	33,365	16,019	0,03	0,481	0,871		0,08	1,281	2,322						
	2	17,138	32,870	15,619	0,01	0,156	0,283	0,577	0,05	0,781	1,415	1,869					
	3	17,042	32,780	15,624					0,16	2,500	4,530		0,55	8,593	15,571		
	4	17,072	32,700	15,515					0,11	1,707	3,093	3,811	0,10	1,552	2,811	9,191	15
	5	16,945	32,590	15,532					0,2	3,106	5,629		0,17	2,640	4,785		
	6	17,206	32,608	15,291					0,12	1,835	3,325	4,477	0,45	6,881	12,468	8,626	
18	1	17,209	33,094	15,770	0,04	0,631	1,143		0,09	1,419	2,572						
	2	17,045	32,564	15,407	0,02	0,308	0,558	0,851	0,06	0,924	1,675	2,123					
	3	16,990	32,502	15,400					0,19	2,926	5,302		0,53	8,162	14,790		
	4	17,183	32,564	15,270					0,14	2,138	3,874	4,588	0,13	1,985	3,597	9,193	18
	5	17,156	32,562	15,295					0,24	3,671	6,651		0,22	3,365	6,097		
	6	17,167	32,369	15,092					0,18	2,717	4,923	5,787	0,46	6,942	12,580	9,338	

21	1	16,907	32,790	15,768	0,04	0,631	1,143		0,10	1,577	2,857							21
	2	16,968	32,448	15,368	0,02	0,307	0,557	0,850	0,07	1,076	1,949	2,403						
	3	17,117	32,616	15,387					0,21	3,231	5,855		0,55	8,463	15,335			
	4	17,042	32,410	15,257					0,18	2,746	4,976	5,416	0,17	2,594	4,700	10,017		
	5	17,054	32,458	15,293					0,22	3,364	6,096		0,41	6,270	11,361			
	6	17,198	32,398	15,090					0,20	3,018	5,469	5,783	0,48	7,243	13,125	12,243		
24	1	16,873	32,728	15,741	0,05	0,787	1,426		0,10	1,574	2,852				0,000			24
	2	17,067	32,545	15,366	0,02	0,307	0,557	0,991	0,07	1,076	1,949	2,401						
	3	16,083	31,559	15,364					0,22	3,380	6,125		0,57	8,758	15,869			
	4	16,896	32,284	15,277					0,18	2,750	4,983	5,554	0,21	3,208	5,813	10,841		
	5	17,212	32,631	15,308					0,28	4,286	7,767		0,34	5,205	9,431			
	6	17,140	32,326	15,076					0,20	3,015	5,464	6,615	0,59	8,895	16,118	12,774		
27	1	17,180	33,073	15,778	0,05	0,789	1,430		0,10	1,578	2,859							27
	2	17,053	32,549	15,384	0,03	0,462	0,836		0,08	1,231	2,230	2,545						
	3	17,164	32,652	15,376					0,23	3,537	6,408		0,58	8,918	16,160			
	4	16,663	32,038	15,264					0,23	3,511	6,361	6,385	0,25	3,816	6,915	11,537		
	5	17,017	32,418	15,290					0,30	4,587	8,312		0,39	5,963	10,805			
	6	16,972	32,159	15,077					0,23	3,468	6,284	7,298	0,60	9,046	16,392	13,599		
30	1	17,067	32,918	15,737	0,04	0,629	1,141		0,09	1,416	2,566							30
	2	16,897	32,361	15,352	0,03	0,461	0,835	0,988	0,08	1,228	2,225	2,396						
	3	17,223	32,729	15,394					0,23	3,541	6,416		0,6	9,236	16,737			
	4	16,837	32,201	15,253					0,21	3,203	5,804	6,110	0,28	4,271	7,739	12,238		
	5	17,058	32,469	15,300					0,31	4,743	8,594		0,45	6,885	12,475			
	6	17,166	32,341	15,066					0,25	3,766	6,825	7,709	0,65	9,793	17,744	15,110		
33	1	17,083	32,950	15,753	0,04	0,630	1,142		0,09	1,418	2,569							33
	2	17,175	32,658	15,371	0,03	0,461	0,836	0,989	0,08	1,230	2,228	2,399						
	3	17,093	32,576	15,371					0,23	3,535	6,406		0,61	9,376	16,990			
	4	17,162	32,542	15,269					0,22	3,359	6,087	6,246	0,31	4,733	8,577	12,784		
	5	17,200	32,604	15,293					0,32	4,894	8,867		0,51	7,799	14,132			
	6	17,176	32,348	15,063					0,25	3,766	6,823	7,845	0,69	10,393	18,832	16,482		
36	1	16,973	32,840	15,753	0,04	0,630	1,142		0,09	1,418	2,569							36
	2	17,148	32,615	15,355	0,02	0,307	0,556	0,849	0,08	1,228	2,226	2,397						
	3	17,007	32,522	15,403					0,24	3,697	6,698		0,64	9,858	17,863			
	4	17,130	32,488	15,247					0,22	3,354	6,078	6,388	0,35	5,337	9,670	13,766		
	5	17,090	32,497	15,296					0,33	5,048	9,146		0,57	8,719	15,798			
	6	16,932	32,123	15,081					0,27	4,072	7,378	8,262	0,73	11,009	19,949	17,874		

39	1	17,146	32,975	15,715	0,03	0,471	0,854		0,08	1,257	2,278						39
	2	17,008	32,444	15,325	0,02	0,306	0,555	0,705	0,07	1,073	1,944	2,111					
	3	16,948	32,409	15,349					0,21	3,223	5,841		0,72	11,052	20,026		
	4	17,214	32,555	15,230					0,21	3,198	5,795	5,818	0,40	6,092	11,039	15,532	
	5	17,014	32,398	15,273					0,31	4,735	8,579		0,68	10,386	18,819		
	6	16,908	32,071	15,054					0,24	3,613	6,547	7,563	0,84	12,645	22,913	20,866	
42	1	16,962	32,797	15,721	0,03	0,472	0,855		0,08	1,258	2,279						42
	2	17,083	32,531	15,337	0,02	0,307	0,556	0,705	0,07	1,074	1,945	2,112					
	3	17,216	32,668	15,341					0,20	3,068	5,559		0,71	10,892	19,736		
	4	17,242	32,590	15,297					0,21	3,200	5,798	5,679	0,45	6,857	12,424	16,080	
	5	17,069	32,455	15,275					0,31	4,735	8,580		0,73	11,151	20,205		
	6	17,143	32,295	15,043					0,23	3,460	6,269	7,425	0,87	13,087	23,714	21,960	
45	1	17,027	32,843	15,702	0,03	0,471	0,854		0,07	1,099	1,992						45
	2	17,210	32,654	15,333	0,02	0,307	0,556	0,705	0,07	1,073	1,945	1,968					
	3	17,012	32,480	15,356					0,20	3,071	5,565		0,73	11,210	20,313		
	4	17,020	32,371	15,240					0,21	3,200	5,799	5,682	0,46	7,011	12,703	16,508	
	5	16,552	31,943	15,280					0,30	4,584	8,306		0,78	11,918	21,596		
	6	17,045	32,200	15,046					0,23	3,461	6,270	7,288	0,89	13,391	24,264	22,930	
48	1	17,134	32,969	15,721	0,02	0,314	0,570		0,07	1,100	1,994						48
	2	17,055	32,473	15,307	0,02	0,306	0,555	0,562	0,07	1,071	1,942	1,968					
	3	16,958	32,418	15,348					0,20	3,070	5,562		0,73	11,204	20,302		
	4	17,249	32,593	15,233					0,20	3,047	5,521	5,541	0,48	7,312	13,249	16,776	
	5	17,143	32,504	15,250					0,32	4,880	8,843		0,81	12,353	22,383		
	6	17,088	32,249	15,052					0,23	3,462	6,273	7,558	0,92	13,847	25,092	23,737	
51	1	16,902	32,717	15,701	0,02	0,314	0,569		0,06	0,942	1,707						51
	2	17,055	32,484	15,318	0,02	0,306	0,555	0,562	0,06	0,919	1,665	1,686					
	3	17,161	32,602	15,330					0,18	2,759	5,000		0,75	11,497	20,833		
	4	16,964	32,291	15,216					0,20	3,043	5,514	5,257	0,50	7,608	13,786	17,310	
	5	17,254	32,640	15,275					0,30	4,583	8,303		0,84	12,831	23,250		
	6	17,027	32,175	15,039					0,22	3,309	5,995	7,149	0,92	13,836	25,070	24,160	
54	1	16,655	32,456	15,687	0,02	0,314	0,568		0,06	0,941	1,705						54
	2	17,138	32,557	15,308	0,02	0,306	0,555	0,562	0,06	0,918	1,664	1,685					
	3	17,147	32,600	15,342					0,18	2,761	5,004		0,76	11,660	21,127		
	4	17,200	32,534	15,223					0,20	3,045	5,517	5,260	0,53	8,068	14,620	17,874	
	5	17,145	32,516	15,260					0,29	4,425	8,019		0,87	13,276	24,057		
	6	17,041	32,180	15,030					0,23	3,457	6,264	7,141	0,94	14,128	25,600	24,828	

57	1	16,473	32,284	15,697	0,02	0,314	0,569		0,06	0,942	1,707						57
	2	17,210	32,641	15,320	0,01	0,153	0,278	0,423	0,06	0,919	1,666	1,686					
	3	17,323	32,765	15,331					0,18	2,760	5,000		0,77	11,805	21,390		
	4	17,163	32,489	15,215					0,19	2,891	5,238	5,119	0,55	8,368	15,164	18,277	
	5	17,165	32,549	15,273					0,28	4,276	7,749		0,90	13,746	24,907		
	6	16,977	32,131	15,045					0,22	3,310	5,997	6,873	0,95	14,292	25,898	25,403	
60	1	16,585	32,393	15,694	0,01	0,157	0,284		0,06	0,942	1,706						60
	2	17,265	32,683	15,307	0,01	0,153	0,277	0,281	0,06	0,918	1,664	1,685					
	3	16,940	32,380	15,329					0,18	2,759	5,000		0,77	11,803	21,387		
	4	17,035	32,375	15,229					0,19	2,894	5,243	5,121	0,58	8,833	16,005	18,696	
	5	17,061	32,433	15,261					0,27	4,120	7,466		0,92	14,040	25,441		
	6	17,231	32,396	15,056					0,21	3,162	5,729	6,598	0,98	14,754	26,735	26,088	
63	1	17,127	32,942	15,701	0,01	0,157	0,285		0,05	0,785	1,423						63
	2	17,210	32,633	15,312	0,01	0,153	0,277	0,281	0,06	0,919	1,665	1,544					
	3	17,175	32,621	15,335					0,17	2,607	4,724		0,81	12,421	22,507		
	4	17,224	32,553	15,218					0,18	2,739	4,964	4,844	0,59	8,979	16,270	19,388	
	5	16,702	32,105	15,292					0,28	4,282	7,758		0,94	14,374	26,046		
	6	17,089	32,242	15,044					0,21	3,159	5,724	6,741	0,95	14,291	25,896	25,971	
66	1	16,833	32,643	15,696	0,01	0,157	0,284		0,05	0,785	1,422						66
	2	17,160	32,577	15,306	0,01	0,153	0,277	0,281	0,05	0,765	1,387	1,404					
	3	17,115	32,588	15,361					0,16	2,458	4,454		0,79	12,135	21,989		
	4	17,140	32,485	15,234					0,19	2,895	5,245	4,849	0,60	9,141	16,563	19,276	
	5	17,197	32,573	15,265					0,28	4,274	7,745		1,00	15,265	27,660		
	6	17,144	32,307	15,054					0,21	3,161	5,728	6,737	0,97	14,602	26,459	27,060	
69	1	17,173	32,988	15,701	0,01	0,157	0,285		0,05	0,785	1,423						69
	2	17,090	32,510	15,309	0,01	0,153	0,277	0,281	0,05	0,765	1,387	1,405					
	3	17,132	32,564	15,321					0,16	2,451	4,442		0,81	12,410	22,486		
	4	17,172	32,494	15,211					0,22	3,347	6,064	5,253	0,76	11,561	20,948	21,717	
	5	17,065	32,442	15,266					0,23	3,511	6,362		0,84	12,823	23,236		
	6	17,072	32,215	15,034					0,2	3,007	5,448	5,905	0,97	14,583	26,424	24,830	
72	1	17,117	32,921	15,690	0,01	0,157	0,284		0,05	0,784	1,422						72
	2	17,121	32,533	15,301	0,01	0,153	0,277	0,281	0,05	0,765	1,386	1,404					
	3	17,119	32,585	15,354					0,17	2,610	4,730		0,82	12,591	22,814		
	4	17,141	32,497	15,245					0,18	2,744	4,972	4,851	0,65	9,909	17,956	20,385	
	5	17,205	32,612	15,296					0,25	3,824	6,929		0,99	15,143	27,439		
	6	17,073	32,246	15,064					0,19	2,862	5,186	6,058	0,99	14,913	27,022	27,231	

Electronic Acknowledgement Receipt

EFS ID:	2879111
Application Number:	11201756
International Application Number:	
Confirmation Number:	3812
Title of Invention:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
First Named Inventor/Applicant Name:	Claus Meese
Customer Number:	26646
Filer:	Willem deWeerd/Theresa Doonan
Filer Authorized By:	Willem deWeerd
Attorney Docket Number:	12961/46103
Receipt Date:	19-FEB-2008
Filing Date:	10-AUG-2005
Time Stamp:	16:06:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	12961_46103_Response_to_Examiners_Interview.pdf	4121841 130099759af492b2591c1f10cf29742325cc33fb	no	67

Warnings:	
Information:	

Total Files Size (in bytes):	4121841

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 03/13/2008

PSTANBAC	SALE	#00000001	Mailroom Dt:	02/19/2008		110600	11201756
		01	FC : 1814	130.00	DA		
		02	FC : 1814	130.00	DA		
		03	FC : 1814	130.00	DA		
		04	FC : 1814	130.00	DA		

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 19 FEB 2008	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

JAB
10/533,683

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 19 FEB 2008	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

JAB
6,858,650

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

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Approved/Disapproved by:

JAB
10/532,836

U.S. Patent and Trademark Office

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/201,756	MEESE ET AL.	

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Date Filed : 19 FEB 2008	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
JAB 6,713,464

U.S. Patent and Trademark Office

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United States Patent and Trademark Office
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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26646 7590 03/26/2008

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/26/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	06/26/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

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Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26646 7590 03/26/2008

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	06/26/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-551000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1_____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2_____ 3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

26646 7590 03/26/2008

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/26/2008

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 156 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 156 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	11/201,756	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *18January 2008 and 19 February 2008*.

2. ☒ The allowed claim(s) is/are *28-43*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *09/700,094* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Zachary C. Tucker/
Primary Examiner, Art Unit 1624

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
11201756	MEESE ET AL.
Examiner	**Art Unit**
Zachary C Tucker	1624

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
514	551	A	0	1	N	37 / 12 (2006.01.01)										
CROSS REFERENCE(S)		A	0	1	N	37 / 44 (2006.01.01)										
		A	6	1	K	31 / 22 (2006.01.01)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)	C	0	7	C	69 / 00 (2006.01.01)										
560	140															

NONE (Assistant Examiner) (Date)		**Total Claims Allowed:** 16	
/Zachary C Tucker/ (Primary Examiner)	14March08 (Date)	O.G. Print Claim(s) 1 and 3	O.G. Print Figure NONE

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11201756	MEESE ET AL.
	Examiner	Art Unit
	Zachary C Tucker	1624

SEARCHED

Class	Subclass	Date	Examiner
514	551	3/14/2008	ZT
560	140	3/14/2008	ZT

SEARCH NOTES

Search Notes	Date	Examiner
CLASS/SUBCLASSES AS INDICATED ON THIS SHEET, CROSS-REFERENCED WITH "TOLTERODINE" OR "FESOTERODINE" OR "MUSCARINIC"	3/14/2008	ZT

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
514	551	3/14/2008	ZT
560	140	3/14/2008	ZT

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	418	560/140 or 514/551	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/03/14 13:32
L2	23	l1 and (diphenylpropylamine or muscarinic or tolterodine or fesoterodine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2008/03/14 13:33

3/14/08 1:43:01 PM
C:\Documents and Settings\ztucker\My Documents\EAST\Workspaces\DIPHENYLPROPYLAMINES CON.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11201756	MEESE ET AL.
	Examiner	Art Unit
	Zachary C Tucker	1624

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/14/2008								
	1									
	2									
	3									
	4									
	5									
	6									
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	29	=								
	30	=								
	31	=								
	32	=								
	33	=								
	34	=								
	35	=								
	36	=								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11201756	MEESE ET AL.
	Examiner	**Art Unit**
	Zachary C Tucker	1624

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=	Allowed	÷	Restricted	I	Interference	O	Objected

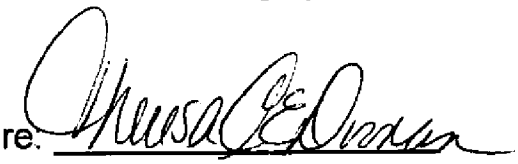
☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/14/2008								
	37	=								
	38	=								
	39	=								
	40	=								
	41	=								
	42	=								
	43	=								

12961/46103
ISSUE FEE

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office via the Office electronic filing system on ***April 14, 2008***

Signature: 

Theresa A.E. Doonan

PART B - FEE(S) TRANSMITTAL

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Theresa A.E. Doonan	(Depositor's name)
/Theresa A.E. Doonan/	(Signature)
April 14, 2008	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	08/10/2005	Claus Meese	12961/46103	3812

TITLE OF INVENTION:
NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
Nonprovisional	NO	$1440.00	$300	$0	$1740.00	06/26/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C.	1624	514-551000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 KENYON & KENYON LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SCHWARZ PHARMA AG

(B) RESIDENCE: (CITY and STATE OR COUNTRY): MONHEIM, GERMANY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 11-0600 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Joseph A Coppola/ Date APRIL 14, 2008

Typed or printed name JOSEPH A. COPPOLA Registration No. 38,413

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	11201756
Filing Date:	10-Aug-2005
Title of Invention:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
First Named Inventor/Applicant Name:	Claus Meese
Filer:	Clifford A. Ulrich/Theresa Doonan
Attorney Docket Number:	12961/46103

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1440	1440
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1740**

Electronic Acknowledgement Receipt

EFS ID:	3148421
Application Number:	11201756
International Application Number:	
Confirmation Number:	3812
Title of Invention:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
First Named Inventor/Applicant Name:	Claus Meese
Customer Number:	26646
Filer:	Clifford A. Ulrich/Theresa Doonan
Filer Authorized By:	Clifford A. Ulrich
Attorney Docket Number:	12961/46103
Receipt Date:	14-APR-2008
Filing Date:	10-AUG-2005
Time Stamp:	15:47:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1740
RAM confirmation Number	1044
Deposit Account	110600
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	12961_46103_Issue_Fee.pdf	80874 44b331519bca94d24932a3f5740e8cac3754e754	no	2
Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8292 2be88cfa76f78a3f991f4a5ec19f588058c429fa	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	89166		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/201,756	06/10/2008	7384980	12961/46103	3812

26646 7590 05/21/2008

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 156 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Claus Meese, Monheim, GERMANY;
Bengt Sparf, Trangsund, SWEDEN;

Kenyon & Kenyon
One Broadway
New York, NY 10004

July 28, 2008

Mail Stop 16
Director of the US Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

To Whom It May Concern,

I have been assigned to reconcile the USPTO's Deposit Account against Kenyon and Kenyon's records. Below are charges that are inconsistent with what we believe is true. I would respectfully ask that you reimburse Kenyon and Kenyon's Deposit Account 110600 for these fees listed below. If there is any other information you need, please feel free to contact me at Jduffy@kenyon.com.

Date		Number	Client/Matter	Code	Amount	IPSS Date	This Equals	Exbis Entry	Notes
17-Mar	3	11201756	12961/46103	1202	$100.00	JKD			This is not valid. There are 19 total claims after the amendment. 8 independent, plus another 5, plus another 6 (multiple). That totals 19. This is not valid

Thank You,

Judy Duffy

Judy Duffy

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 03/17/2008

PSTANBAC	SALE	#00000003	Mailroom Dt:	01/18/2008		110600	11201756
		01	FC : 1202	100.00	DA		
		02	FC : 1201	630.00	DA		
		03	FC : 1203	370.00	DA		

Adjustment date: 07/30/2008 HDESTA1
03/17/2008 PSTANBAC 00000003 110600 11201756
01 FC:1202 100.00 CR

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	ACCORD HEALTHCARE INC., USA

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	AMERIGEN PHARMACEUTICALS, INC. and AMERIGEN PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	IMPAX LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

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Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/28/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	LUPIN LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	US 7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	US 7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	US 7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	US 8,338,478 B2	12/25/2012	UCB Pharma GmbH

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	AMNEAL PHARMACEUTICALS, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/21/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	SANDOZ INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-1110-GMS	6/21/2013	of Delaware

PLAINTIFF	DEFENDANT
Pfizer Inc. and UCB Pharma GmbH	Alkem Laboratories Ltd.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 6,858,650 B1	2/22/2005	UCB PHarma GmbH
2	US 7,384,980 B2	6/10/2008	UCB PHarma GmbH
3	US 7,855,230 B2	12/21/2010	UCB PHarma GmbH
4	US 7,985,772 B2	7/26/2011	UCB PHarma GmbH
5	US 8,338,478 B2	12/25/2012	UCB PHarma GmbH

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DATE INCLUDED	INCLUDED BY ☐ Amendment ☑ Answer ☐ Cross Bill ☐ Other Pleading		
7/15/2013			
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 7,807,715 B2	10/5/2010	UCB PHarma GmbH
2	US 8,088,398 B2	1/3/2012	UCB PHarma GmbH
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In the above—entitled case, the following decision has been rendered or judgement issued:

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/11/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	HETERO USA INC. and HETERO LABS LIMITED

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/11/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC. and UCB PHARMA GMBH	APOTEX INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,858,650 B1	2/22/2005	UCB Pharma GmbH
2	7,384,980 B2	6/10/2008	UCB Pharma GmbH
3	7,855,230 B2	12/21/2010	UCB Pharma GmbH
4	7,985,772 B2	7/26/2011	UCB Pharma GmbH
5	8,338,478 B2	12/25/2012	UCB Pharma GmbH

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT		
CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
C.A. No. 13-2022-GMS	12/11/2013	District of Delaware

PLAINTIFF	DEFENDANT
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
2/3/2014	☐ Amendment ☑ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,807,715 B2	10/5/2010	UCB Pharma GmbH
2	8,088,398 B2	1/3/2012	UCB Pharma GmbH
3	8,501,723 B2	8/6/2013	UCB Pharma GmbH
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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