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- (73) Patenthaver: **Novartis AG, Lichtstrasse 35, 4056 Basel, Schweiz**
- (72) Opfinder: **RUEGGER, Colleen, Novartis AG, Lichtstrasse 35, 4056 Basel, Schweiz**  
**AMBUEHL, Michael, Novartis AG, Lichtstrasse 35, 4056 Basel, Schweiz**
- (74) Fuldmægtig i Danmark: **Budde Schou A/S, Dronningens Tværgade 30, 1302 København K, Danmark**
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**W.A Ritschel ET AL: "Die Tablette" In: "der Pharmazeutische Betrieb", 1 January 2002 (2002-01-01), XP055464317, ISBN: 978-3-87193-228-1 page 68,**



## DESCRIPTION

[0001] The present invention relates to the use of a binary blend consisting of :

1. (i) 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol (FTY720) in free form or as a pharmaceutically acceptable salt thereof, and
2. (ii) one excipient selected from the group consisting of:  
Lactose, Hydroxypropyl methylcellulose (HPMC), croscarmellose sodium and starch

[0002] in the preparation of a medicament for use in the treatment of organ or tissue transplant rejection, graft versus host disease, autoimmune diseases, inflammatory conditions, viral myocarditis, and viral diseases caused by viral myocarditis or cancers, where the binary blend is free from impurities.

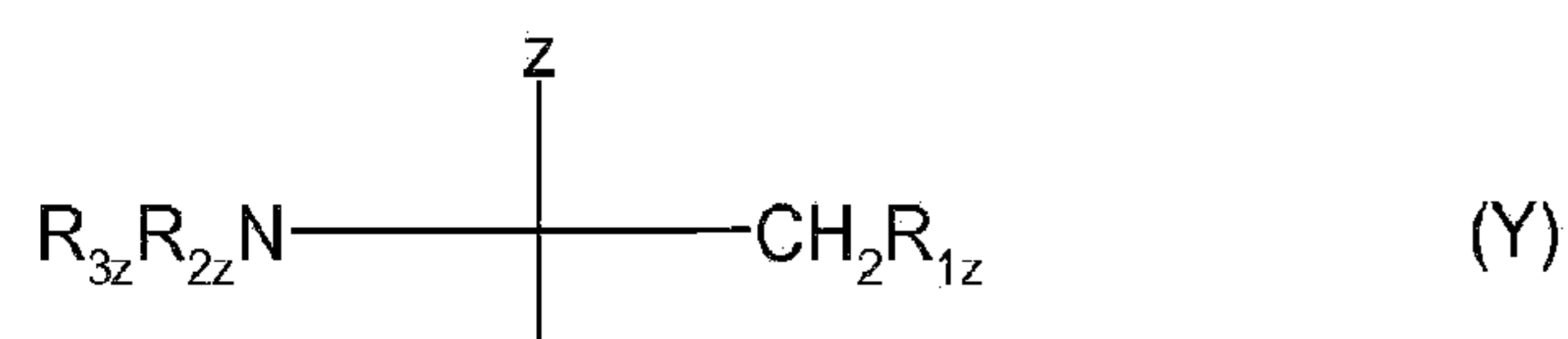
[0003] For reference purposes, , the present disclosure relates to stable compositions comprising a sphingosine 1 phosphate (S1P) receptor modulator suitable for use as a dosage form.

[0004] S1P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-amino- propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula Y.

[0005] WO 2004/089341 relates to compositions with 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol (FTY720) and sugar alcohols. WO 2007/021666 A2 refers to concentrates in solution and thus the ingredients are selected from specific ones only, especially propylene glycol and optionally glycerin. WO 2008/037421 discloses compositions with FTY720. WO 2005/025553 relates to pharmaceutical compositions with FTY720 and these are described without defining a specific number of ingredients.

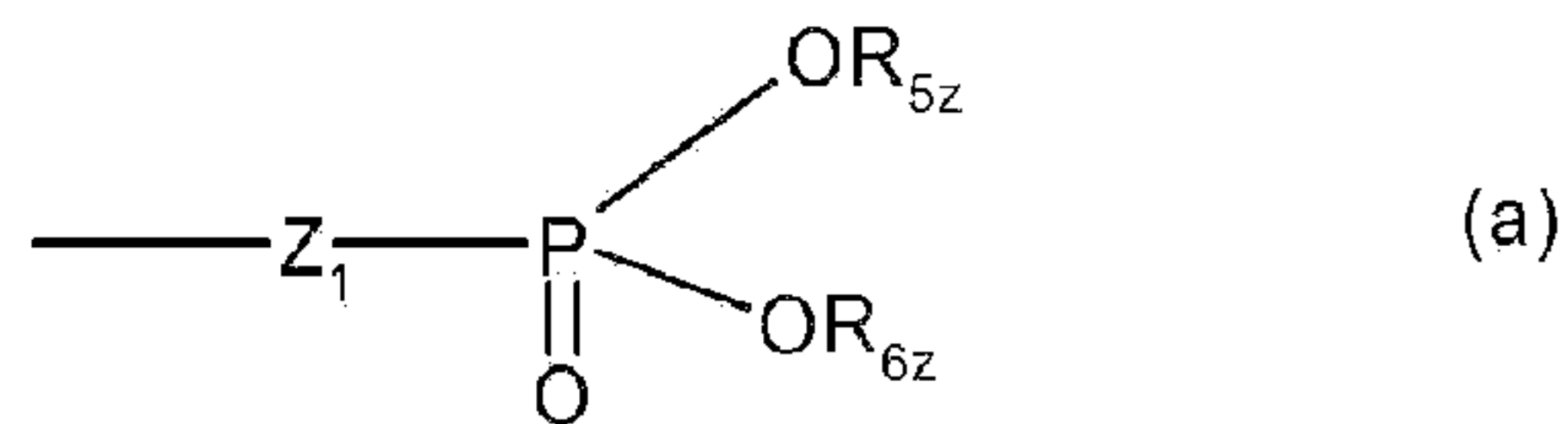
### ***S1P receptor modulators***

[0006] For disclosure purposes, sphingosine-1 phosphate (hereinafter "S1P") is a natural serum lipid. Presently there are eight known S1P receptors, namely S1P1 to S1P8. S1 P receptor modulators are typically sphingosine analogues, such as 2-substituted 2-aminopropane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula Y



wherein Z is H, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, phenyl, phenyl substituted by OH, C<sub>1-6</sub>alkyl

substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH, or CH<sub>2</sub>-R<sub>4z</sub> wherein R<sub>4z</sub> is OH, acyloxy or a residue of formula (a)



wherein Z<sub>1</sub> is a direct bond or O, preferably O;

each of R<sub>5z</sub> and R<sub>6z</sub>, independently, is H, or C<sub>1-4</sub>alkyl optionally substituted by 1, 2 or 3 halogen atoms;

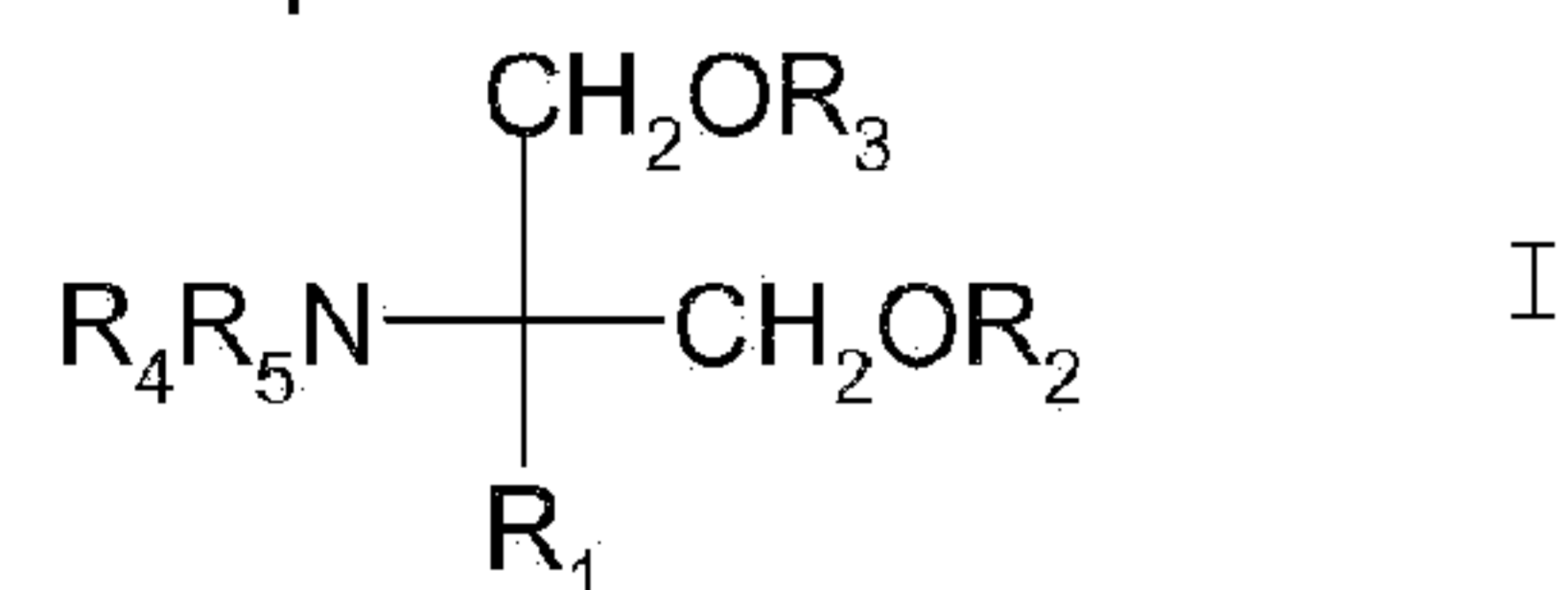
R<sub>1z</sub> is OH, acyloxy or a residue of formula (a); and each of R<sub>2z</sub> and R<sub>3z</sub> independently, is H, C<sub>1-4</sub>alkyl or acyl.

**[0007]** Group of formula Y is a functional group attached as a terminal group to a moiety which may be hydrophilic or lipophilic and comprise one or more aliphatic, alicyclic, aromatic and/or heterocyclic residues, to the extent that the resulting molecule wherein at least one of Z and R<sub>1z</sub> is or comprises a residue of formula (a), signals as an agonist at one of more sphingosine-1-phosphate receptor.

**[0008]** S1P receptor modulators are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into G $\alpha$ -GTP and G $\beta\gamma$ -GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

**[0009]** Examples of appropriate S1P receptor modulators, comprising a group of formula Y are, for example:

Compounds as disclosed in EP627406A1, e.g. a compound of formula I



wherein R<sub>1</sub> is a straight- or branched (C<sub>12-22</sub>) chain

- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR<sub>6</sub>, wherein R<sub>6</sub> is H, C<sub>1-4</sub>alkyl, aryl-C<sub>1-4</sub>alkyl, acyl or (C<sub>1-4</sub>alkoxy)carbonyl, and carbonyl, and/or
  - which may have as a substituent C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy, C<sub>2-4</sub>alkynyloxy, arylC<sub>1-4</sub>alkyl-oxy, acyl, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>alkylthio, acylamino, (C<sub>1-4</sub>alkoxy)carbonyl, (C<sub>1-4</sub>alkoxy)-carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl)carbamoyl, nitro,

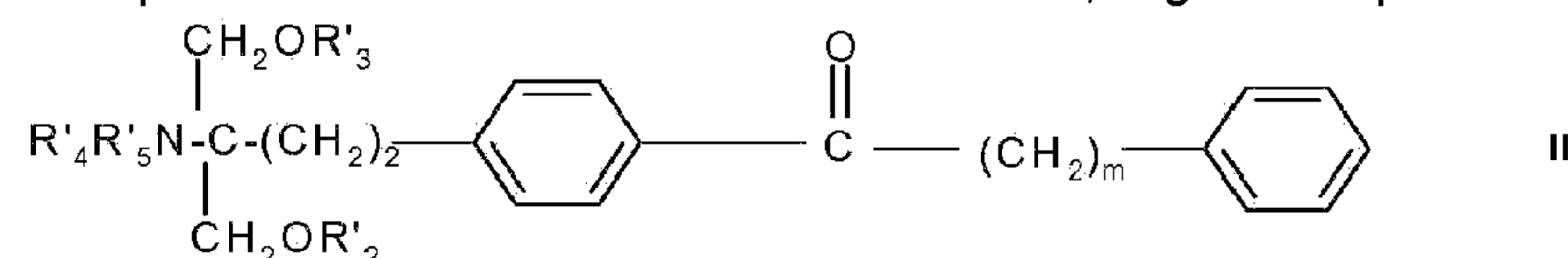
halogen, amino, hydroxyimino, hydroxy or carboxy; or

R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain; or
  - a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
  - a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
  - a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
  - a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
  - phenyl-C<sub>1-14</sub>alkoxy, halophenyl-C<sub>1-4</sub>alkoxy, phenyl-C<sub>1-14</sub>alkoxy-C<sub>1-14</sub>alkyl, phenoxy-C<sub>1-4</sub>alkoxy or phenoxy-C<sub>1-4</sub>alkyl,
  - cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
  - heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
  - heterocyclic C<sub>6-20</sub>alkyl or
  - heterocyclic alkyl substituted by C<sub>2-20</sub>alkyl,
- and wherein  
the alkyl moiety may have
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and
  - as a substituent C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy, C<sub>2-4</sub>alkynyloxy, arylC<sub>1-4</sub>alkyloxy, acyl, C<sub>1-4</sub>alkyl-amino, C<sub>1-4</sub>alkylthio, acylamino, (C<sub>1-4</sub>alkoxy)carbonyl, (C<sub>1-4</sub>alkoxy)carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

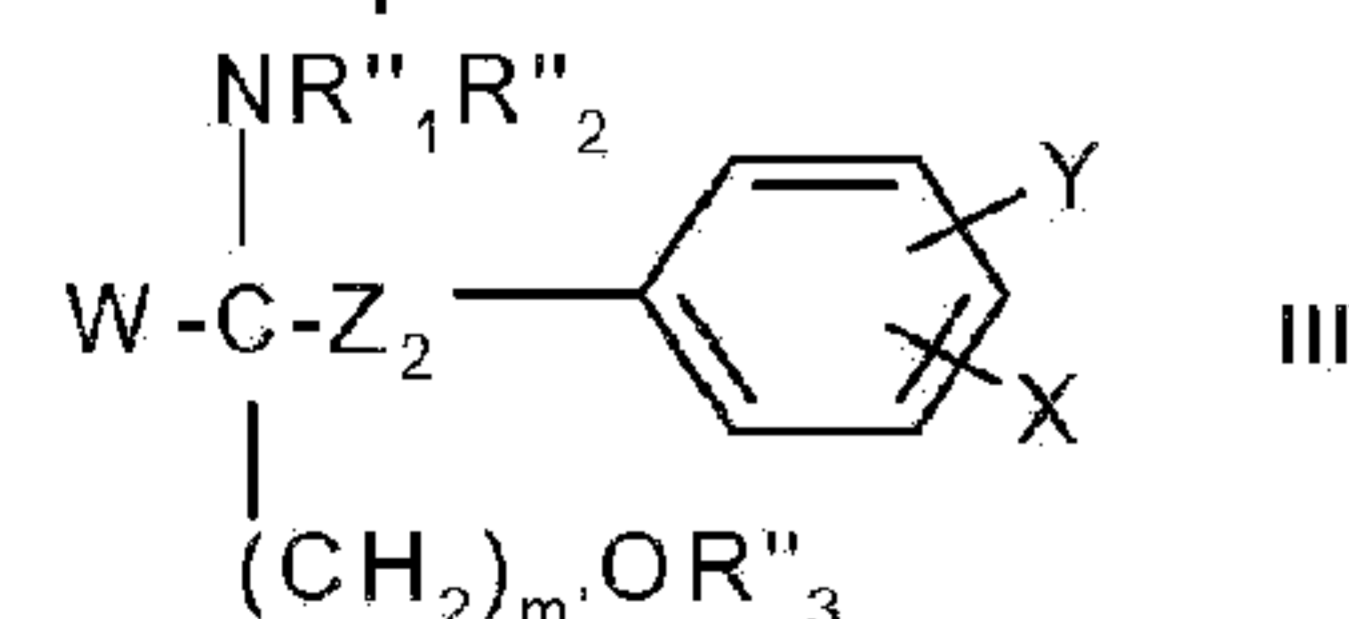
each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, independently, is H, C<sub>1-4</sub> alkyl or acyl  
or a pharmaceutically acceptable salt or hydrate thereof;

Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



wherein m is 1 to 9 and each of R'<sub>2</sub>, R'<sub>3</sub>, R'<sub>4</sub> and R'<sub>5</sub>, independently, is H, C<sub>1-6</sub>alkyl or acyl, or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III



wherein W is H; C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl; unsubstituted or by OH substituted phenyl; R''<sub>4</sub>O(CH<sub>2</sub>)<sub>n</sub>; or C<sub>1-6</sub>alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C<sub>3-8</sub>cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or

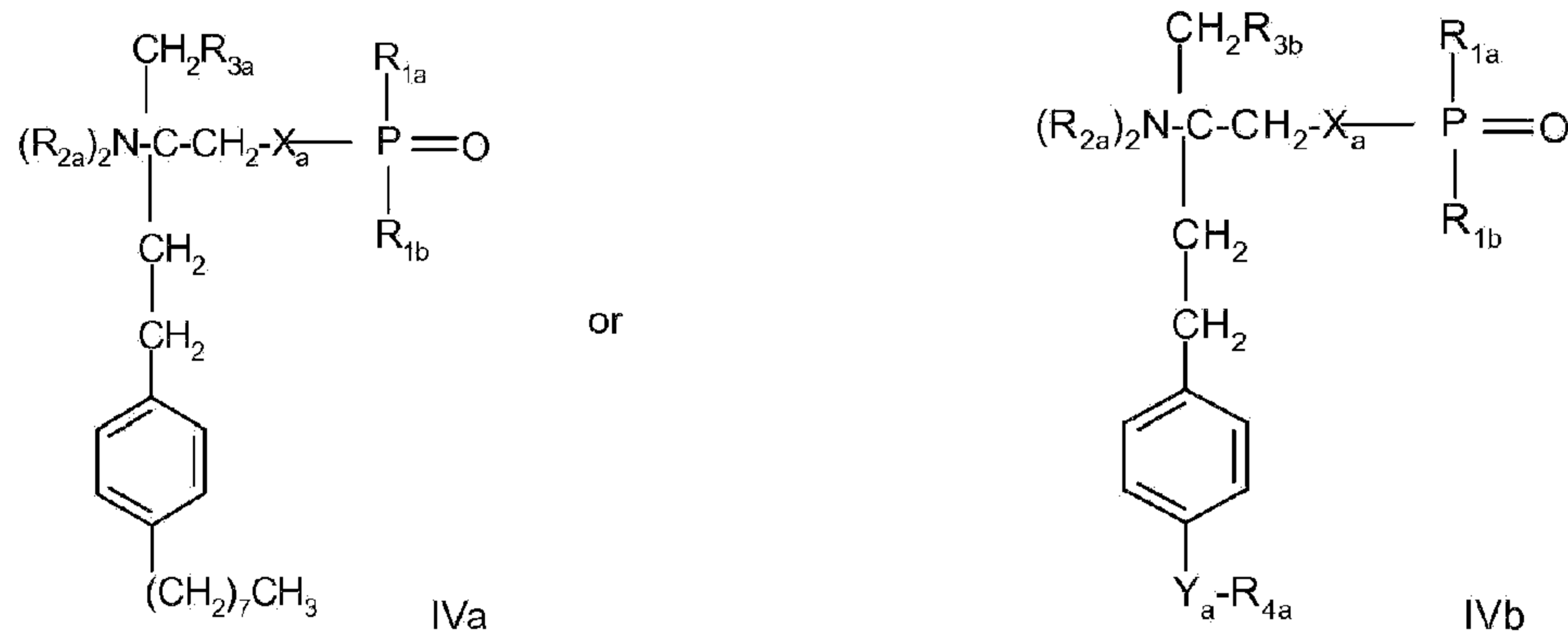
unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, oxo, haloC<sub>1-6</sub>alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl and halogen; Y is H, C<sub>1-6</sub>alkyl, OH, C<sub>1-6</sub>alkoxy, acyl, acyloxy, amino, C<sub>1-6</sub>alkylamino, acylamino, haloC<sub>1-6</sub>alkyl or halogen, Z<sub>2</sub> is a single bond or a straight chain alkylene having a number of carbon atoms of q,

each of p and q, independently, is an integer of 1 to 20, with the proviso of 6 ≤ p+q ≤ 23, m' is 1, 2 or 3, n is 2 or 3,

each of R''<sub>1</sub>, R''<sub>2</sub>, R''<sub>3</sub> and R''<sub>4</sub>, independently, is H, C<sub>1-4</sub>alkyl or acyl,

or a pharmaceutically acceptable salt or hydrate thereof,

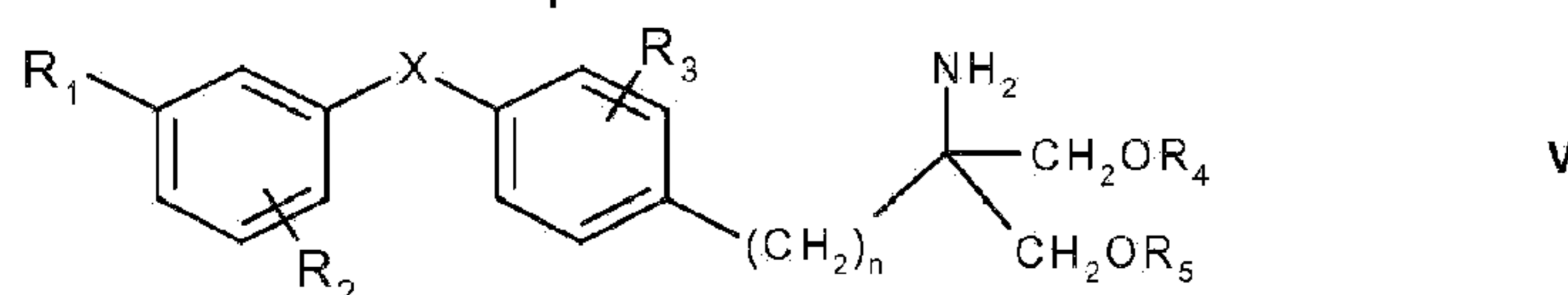
Compounds as disclosed in WO02/18395, e.g. a compound of formula IVa or IVb



wherein X<sub>a</sub> is O, S, NR<sub>1s</sub> or a group -(CH<sub>2</sub>)<sub>n<sub>a</sub></sub>-, which group is unsubstituted or substituted by 1 to 4 halogen; n<sub>a</sub> is 1 or 2, R<sub>1s</sub> is H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>1a</sub> is H, OH, (C<sub>1-4</sub>)alkyl or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R<sub>1b</sub> is H, OH or (C<sub>1-4</sub>)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R<sub>2a</sub> is independently selected from H or (C<sub>1-4</sub>)alkyl, which alkyl is unsubstituted or substituted by halogen; R<sub>3a</sub> is H, OH, halogen or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R<sub>3b</sub> is H, OH, halogen, (C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C<sub>1-4</sub>)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y<sub>a</sub> is -CH<sub>2</sub>-, -C(O)-, -CH(OH)-, -C(=NOH)-, O or S, and R<sub>4a</sub> is (C<sub>4-14</sub>)alkyl or (C<sub>4-14</sub>)alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

Amino alcohol compounds of formula V

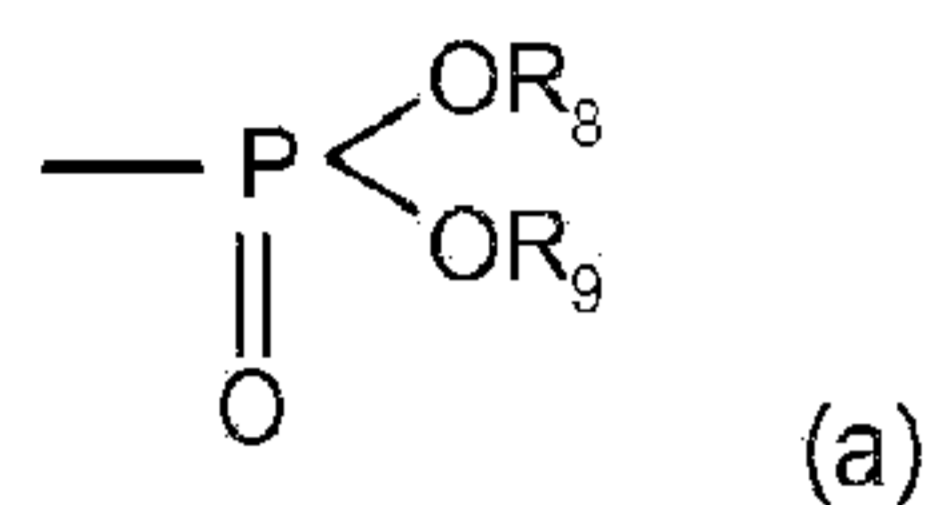


wherein X is O, S, SO or SO<sub>2</sub>;

$R_1$  is halogen, trihalomethyl, OH,  $C_{1-7}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethoxy, phenoxy, cyclohexylmethoxy, pyridylmethoxy, cinnamyloxy, naphthylmethoxy, phenoxymethyl,  $CH_2-OH$ ,  $CH_2-CH_2-OH$ ,  $C_{1-4}$ alkylthio,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl, benzylthio, acetyl, nitro or cyano, or phenyl, phenyl $C_{1-4}$ alkyl or phenyl- $C_{1-4}$ alkoxy each phenyl group thereof being optionally substituted by halogen,  $CF_3$ ,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy;

$R_2$  is H, halogen, trihalomethyl,  $C_{1-4}$ alkoxy,  $C_{1-7}$ alkyl, phenethyl or benzyloxy;

$R_3$  H, halogen,  $CF_3$ , OH,  $C_{1-7}$ alkyl,  $C_{1-4}$ alkoxy, benzyloxy, phenyl or  $C_{1-4}$ alkoxymethyl; each of  $R_4$  and  $R_5$ , independently is H or a residue of formula (a)

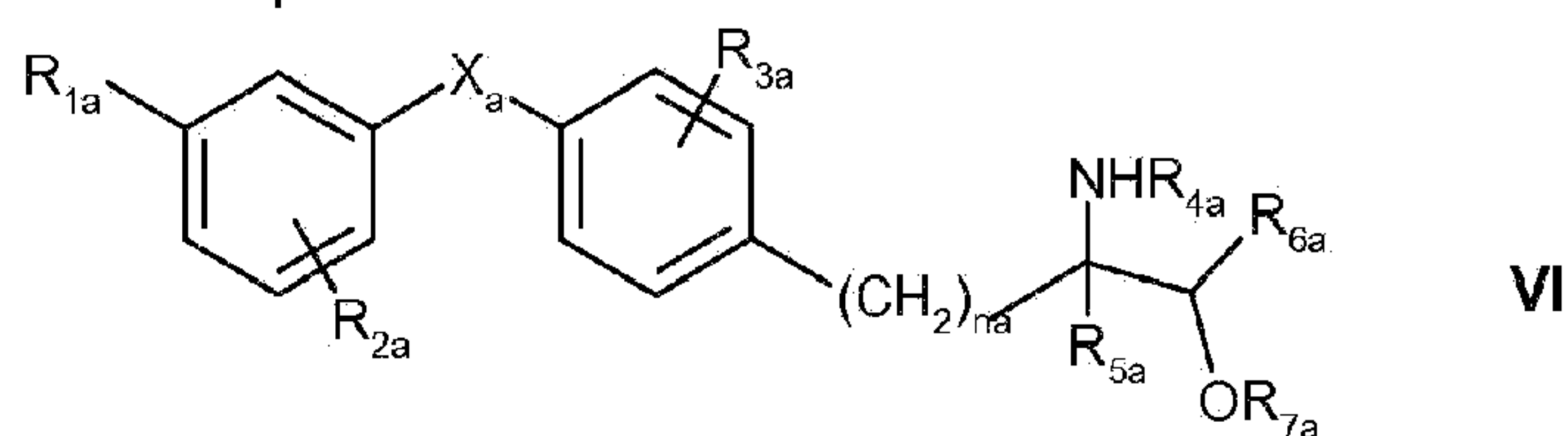


wherein each of  $R_8$  and  $R_9$ , independently, is H or  $C_{1-4}$ alkyl optionally substituted by halogen; and

$n$  is an integer from 1 to 4;

or a pharmaceutically acceptable salt thereof;

or a compound of formula VI



wherein

$R_{1a}$

is halogen, trihalomethyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl, aralkyl, optionally substituted phenoxy or aralkyloxy;

$R_{2a}$

is H, halogen, trihalomethyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, aralkyl or aralkyloxy;

$R_{3a}$

is H, halogen,  $CF_3$ ,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio or benzyloxy;

$R_{4a}$

is H,  $C_{1-4}$ alkyl, phenyl, optionally substituted benzyl or benzoyl, or lower aliphatic  $C_{1-5}$ acyl;

$R_{5a}$

is H, monohalomethyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy-methyl,  $C_{1-4}$ alkyl-thiomethyl, hydroxyethyl, hydroxypropyl, phenyl, aralkyl,  $C_{2-4}$ alkenyl or -alkynyl;

$R_{6a}$

is H or C<sub>1-4</sub>alkyl;

R<sub>7a</sub>

is H, C<sub>1-4</sub>alkyl or a residue of formula (a) as defined above,

X<sub>a</sub>

is O, S, SO or SO<sub>2</sub>; and

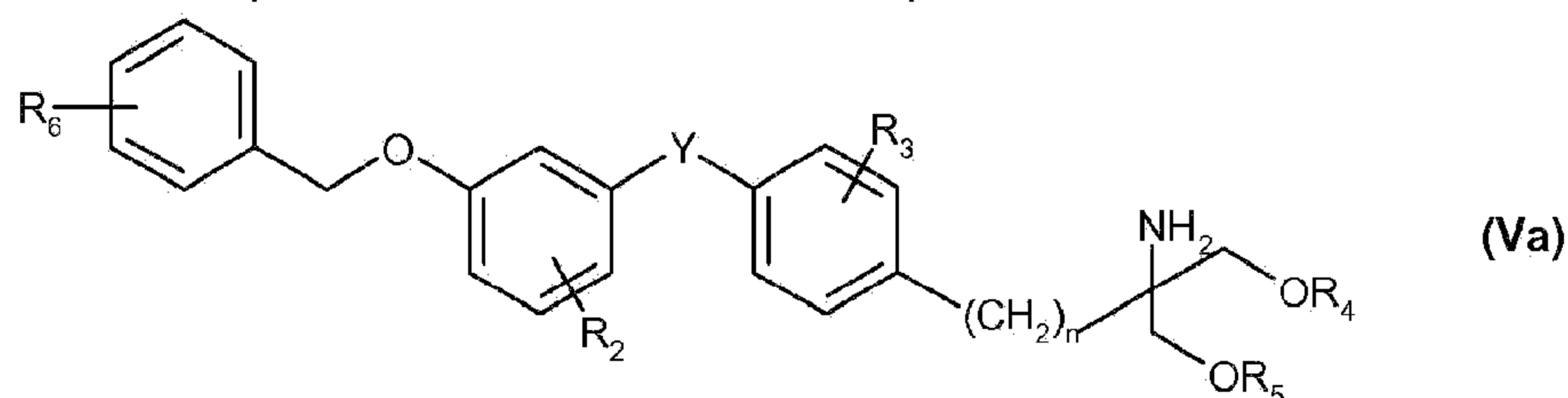
n<sub>a</sub>

is an integer of 1 to 4;

or a pharmaceutically acceptable salt thereof.

With regard to the compounds of formulae (I) and (II), the term "halogen" encompasses fluorine, chlorine, bromine and iodine. The term "trihalomethyl group" encompasses trifluoromethyl and trichloromethyl. "C<sub>1-7</sub> alkyl" encompasses straight-chained or branched alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, pentyl, hexyl or heptyl. The phrase "substituted or unsubstituted phenoxy group" encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy. The term "aralkyl group" as in "aralkyl group" or "aralkyloxy group" encompasses benzyl, diphenylmethyl, phenethyl and phenylpropyl. Any alkyl moiety as present in "C<sub>1-4</sub>alkoxy", "C<sub>1-4</sub>alkylthio", "C<sub>1-4</sub>alkylsulfinyl" or "C<sub>1-4</sub>alkylsulfonyl" encompasses straight-chained or branched C<sub>1-4</sub>alkyl, e.g. methyl, ethyl, propyl, isopropyl or butyl. The phrase "substituted or unsubstituted aralkyl group" encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1-4 carbon atoms, or lower alkoxy having 1-4 carbon atoms.

Other compounds of formula V are compounds of formula Va



wherein

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and n are as defined above; and Y is O or S and

R<sub>6</sub> is hydrogen, halogen, C<sub>1-7</sub>alkyl, C<sub>1-4</sub>alkoxy or trifluoromethyl.

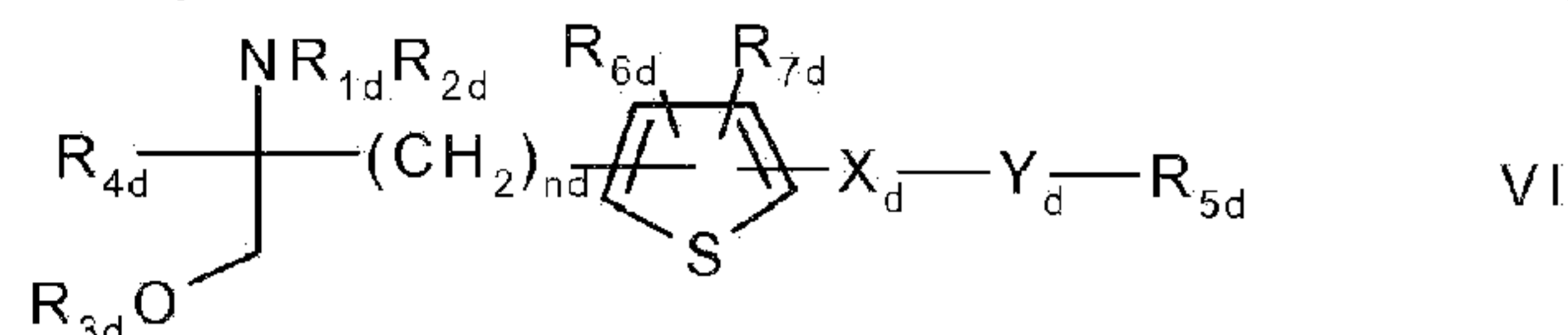
**[0010]** Compounds of formulae V and Va are known and are disclosed e.g. in WO03/029205, WO 03/029184 and WO04/026817, respectively, the phosphorylated derivatives being disclosed e.g. in WO04/074297. Compounds disclosed may be prepared as disclosed in the cited references herein.



[0011] Phosphorylated derivatives of compounds described herein can be prepared utilizing the procedures for synthesizing phosphorylated compounds described known in the art, e.g., in WO 2005/021503 (see, e.g., pages 11 and 12).

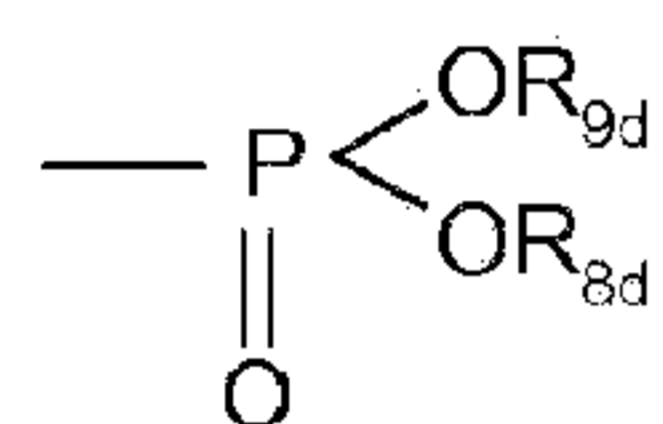
[0012] Optically active compounds of and phosphorylated derivatives thereof can be prepared in high purity utilizing procedure described in the art, e.g. in Hinterding et al., Synthesis, Vol. 11, pp.1667-1670 (2003).

Compounds as disclosed in WO02/06268A1, e.g. a compound of formula VI



wherein each of  $R_{1d}$  and  $R_{2d}$ , independently, is H or an amino-protecting group;

$R_{3d}$  is hydrogen, a hydroxy-protecting group or a residue of formula



$R_{4d}$  is  $C_{1-4}$ alkyl;

$n_d$  is an integer of 1 to 6;

$X_d$  is ethylene, vinylene, ethynylene, a group having a formula - D-CH<sub>2</sub>- (wherein D is carbonyl, -CH(OH)-, O, S or N), aryl or aryl substituted by up to three substituents selected from group a as defined hereinafter;

$Y_d$  is single bond,  $C_{1-10}$ alkylene,  $C_{1-10}$ alkylene which is substituted by up to three substituents selected from groups a and b,  $C_{1-10}$ alkylene having O or S in the middle or end of the carbon chain, or  $C_{1-10}$ alkylene having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;

$R_{5d}$  is hydrogen,  $C_{3-6}$ cycloalkyl, aryl, heterocyclic group,  $C_{3-6}$ cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocyclic group substituted by up to three substituents selected from groups a and b;

each of  $R_{6d}$  and  $R_{7d}$ , independently, is H or a substituents selected from group a;

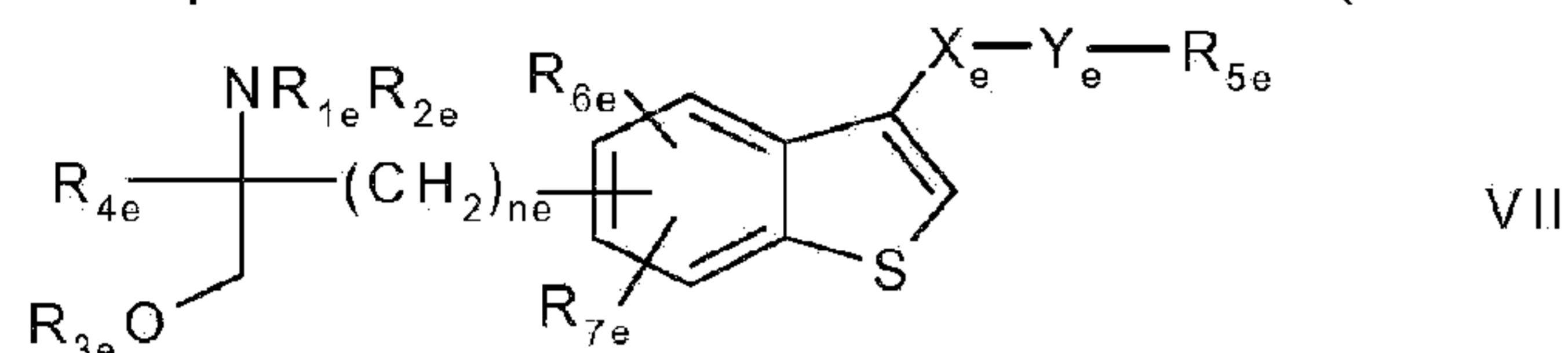
each of  $R_{8d}$  and  $R_{9d}$ , independently, is H or  $C_{1-4}$ alkyl optionally substituted by halogen;

<group a > is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkylthio, carboxyl, lower alkoxy carbonyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkylamino, di- $C_{1-4}$ alkylamino, acylamino, cyano or nitro; and

<group b > is C<sub>3-6</sub>cycloalkyl, aryl or heterocyclic group, each being optionally substituted by up to three substituents selected from group a;

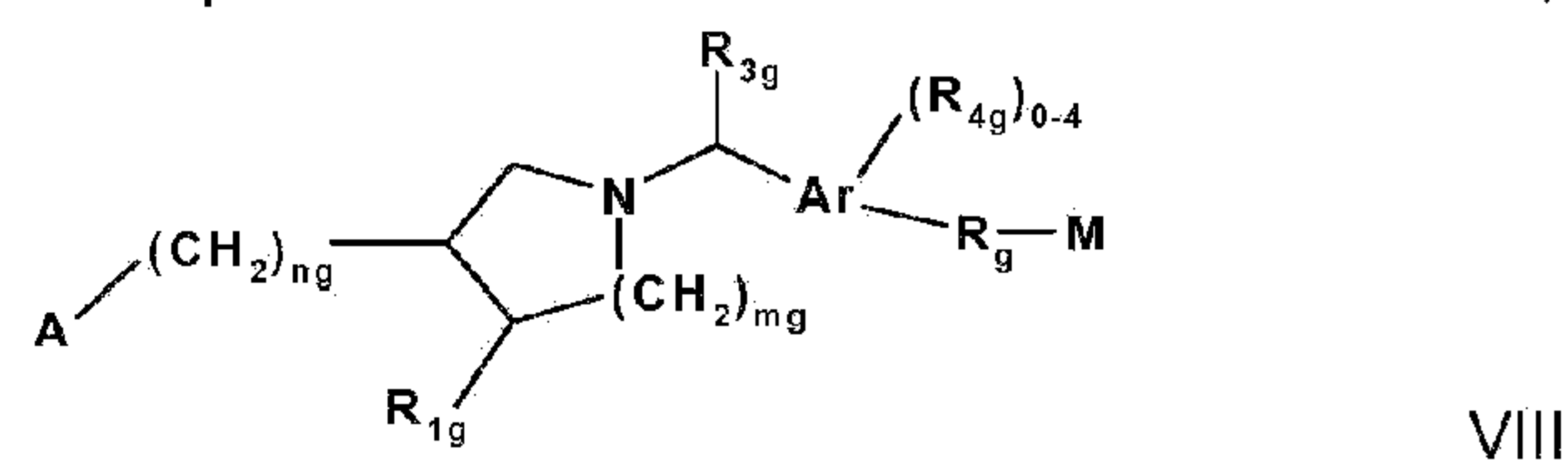
with the proviso that when R<sub>5d</sub> is hydrogen, Y<sub>d</sub> is either a single bond or linear C<sub>1-10</sub> alkylene, or a pharmacologically acceptable salt, ester or hydrate thereof;

-Compounds as disclosed in JP-14316985 (JP2002316985), e.g. a compound of formula VII



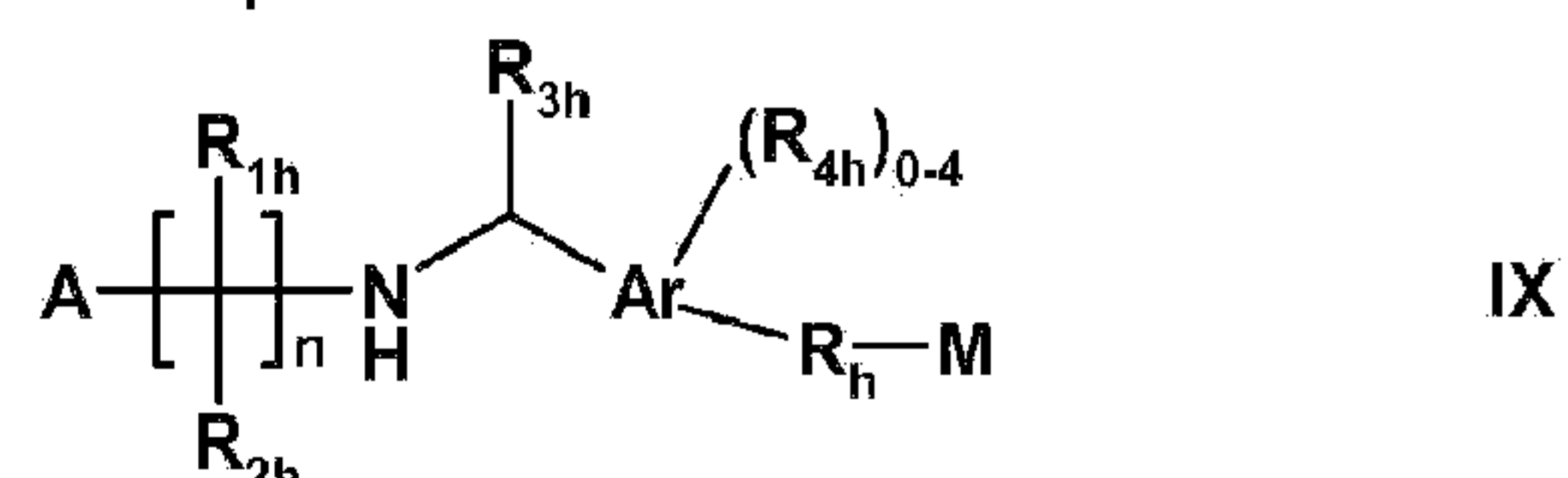
wherein R<sub>1e</sub>, R<sub>2e</sub>, R<sub>3e</sub>, R<sub>4e</sub>, R<sub>5e</sub>, R<sub>6e</sub>, R<sub>7e</sub>, n<sub>e</sub>, X<sub>e</sub> and Y<sub>e</sub> are as disclosed in JP-14316985; or a pharmacologically acceptable salt, ester or hydrate thereof;

-Compounds as disclosed in WO03/062252A1, e.g. a compound of formula VIII



wherein Ar is phenyl or naphthyl; each of m<sub>g</sub> and n<sub>g</sub> independently is 0 or 1; A is selected from COOH, PO<sub>3</sub>H<sub>2</sub>, PO<sub>2</sub>H, SO<sub>3</sub>H, PO(C<sub>1-3</sub>alkyl)OH and 1*H*-tetrazol-5-yl; each of R<sub>1g</sub> and R<sub>2g</sub> independently is H, halogen, OH, COOH or C<sub>1-4</sub>alkyl optionally substituted by halogen; R<sub>3g</sub> is H or C<sub>1-4</sub>alkyl optionally substituted by halogen or OH; each R<sub>4g</sub> independently is halogen, or optionally halogen substituted C<sub>1-4</sub>alkyl or C<sub>1-3</sub>alkoxy; and each of R<sub>g</sub> and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1; or a pharmacologically acceptable salt, solvate or hydrate thereof;

-Compounds as disclosed in WO 03/062248A2, e.g. a compound of formula IX

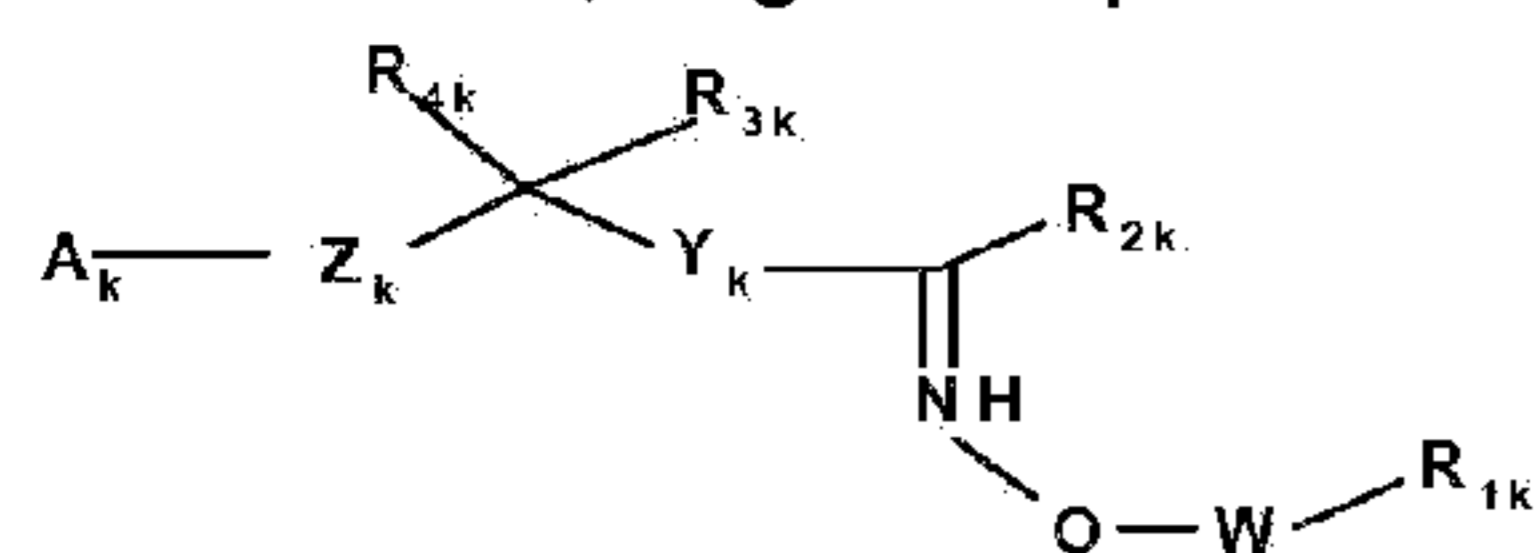


wherein Ar is phenyl or naphthyl; n is 2, 3 or 4; A is COOH, 1*H*-tetrazol-5-yl, PO<sub>3</sub>H<sub>2</sub>, PO<sub>2</sub>H<sub>2</sub>, -SO<sub>3</sub>H or PO(R<sub>5h</sub>)OH wherein R<sub>5h</sub> is selected from C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, phenyl, -CO-C<sub>1-3</sub>alkoxy and -CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R<sub>1h</sub> and R<sub>2h</sub> independently is H, halogen, OH, COOH, or optionally halogeno substituted C<sub>1-6</sub>alkyl or phenyl; R<sub>3h</sub> is H or C<sub>1-4</sub>alkyl optionally substituted by halogen and/ OH; each R<sub>4h</sub> independently is halogen, OH, COOH, C<sub>1-4</sub>alkyl, S(O)<sub>0,1 or 2</sub>C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, C<sub>3-6</sub>cycloalkoxy, aryl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R<sub>h</sub> and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2

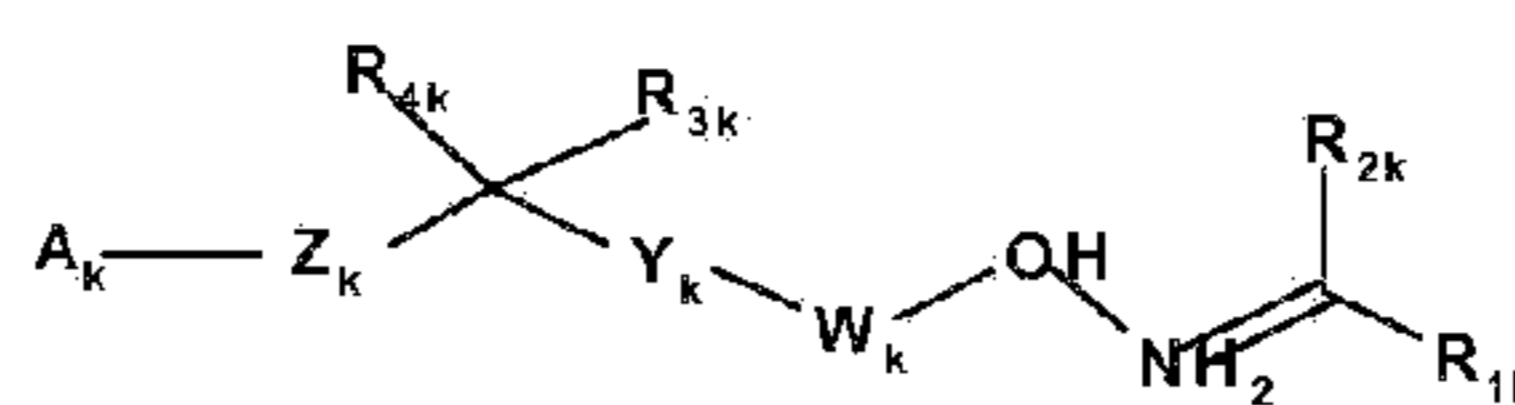
or a pharmacologically acceptable salt, solvate or hydrate thereof.

- Compounds as disclosed in WO 04/103306A, WO 05/000833, WO 05/103309 or WO

05/113330, e.g. compounds of formula Xa or Xb



Xa



Xb

wherein

$A_k$  is  $\text{COOR}_{5k}$ ,  $\text{OPO}(\text{OR}_{5k})_2$ ,  $\text{PO}(\text{OR}_{5k})_2$ ,  $\text{SO}_2\text{OR}_{5k}$ ,  $\text{POR}_{5k}\text{OR}_{5k}$  or 1H-tetrazol-5-yl,  $R_{5k}$  being H or  $\text{C}_{1-6}$ alkyl;

$W_k$  is a bond,  $\text{C}_{1-3}$ alkylene or  $\text{C}_{2-3}$ alkenylene;

$Y_k$  is  $\text{C}_{6-10}$ aryl or  $\text{C}_{3-9}$ heteroaryl, optionally substituted by 1 to 3 radicals selected from halogene, OH,  $\text{NO}_2$ ,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy; halo-substituted  $\text{C}_{1-6}$ alkyl and halo-substituted  $\text{C}_{1-6}$ alkoxy;

$Z_k$  is a heterocyclic group as indicated in WO 04/103306A, e.g. azetidine;

$R_{1k}$  is  $\text{C}_{6-10}$ aryl or  $\text{C}_{3-9}$ heteroaryl, optionally substituted by  $\text{C}_{1-6}$ alkyl,  $\text{C}_{6-10}$ aryl,  $\text{C}_{6-10}$ aryl $\text{C}_{1-4}$ alkyl,  $\text{C}_{3-9}$ heteroaryl,  $\text{C}_{3-9}$ heteroaryl $\text{C}_{1-4}$ alkyl,  $\text{C}_{3-8}$ cycloalkyl,  $\text{C}_{3-8}$ cycloalkyl $\text{C}_{1-4}$ alkyl,  $\text{C}_{3-8}$ heterocycloalkyl or  $\text{C}_{3-8}$ heterocycloalkyl $\text{C}_{1-4}$ alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of  $R_{1k}$  may be substituted by 1 to 5 groups selected from halogen,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy and halo substituted- $\text{C}_{1-6}$ alkyl or - $\text{C}_{1-6}$ alkoxy;

$R_{2k}$  is H,  $\text{C}_{1-6}$ alkyl, halo substituted  $\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkenyl or  $\text{C}_{2-6}$ alkynyl; and

each of  $R_{3k}$  or  $R_{4k}$ , independently, is H, halogen, OH,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy or halo substituted  $\text{C}_{1-6}$ alkyl or  $\text{C}_{1-6}$ alkoxy;

and the N-oxide derivatives thereof or prodrugs thereof,

or a pharmacologically acceptable salt, solvate or hydrate thereof.

**[0013]** The compounds of formulae I to Xb may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formulae III to VIII include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the combination of the present invention encompass hydrate and solvate forms.

**[0014]** Acyl as indicated above may be a residue  $R_y$ -CO- wherein  $R_y$  is  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl, phenyl or phenyl- $C_{1-4}$ alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

**[0015]** Aryl may be phenyl or naphthyl, preferably phenyl.

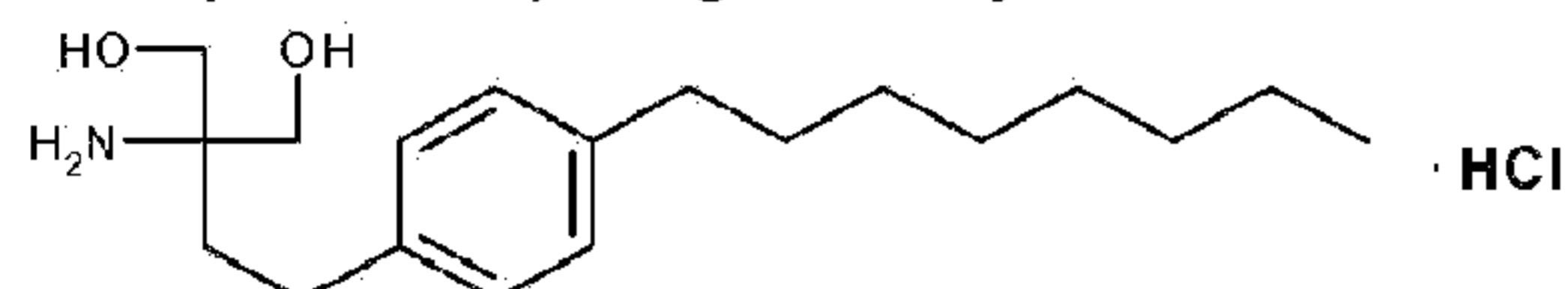
**[0016]** When in the compounds of formula I the carbon chain as  $R_1$  is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by an optionally substituted phenylene, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy.

**[0017]** Preferred compounds of formula I are those wherein  $R_1$  is  $C_{13-20}$ alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein  $R_1$  is phenylalkyl substituted by  $C_{6-14}$ -alkyl chain optionally substituted by halogen and the alkyl moiety is a  $C_{1-6}$ alkyl optionally substituted by hydroxy. More preferably,  $R_1$  is phenyl- $C_{1-6}$ alkyl substituted on the phenyl by a straight or branched, preferably straight,  $C_{6-14}$ alkyl chain. The  $C_{6-14}$ alkyl chain may be in ortho, meta or para, preferably in para.

**[0018]** Preferably each of  $R_2$  to  $R_5$  is H.

**[0019]** In the above formula of VII "heterocyclic group" represents a 5- to 7 membered heterocyclic group having 1 to 3 heteroatoms selected from S, O and N. Examples of such heterocyclic groups include the heteroaryl groups indicated above, and heterocyclic compounds corresponding to partially or completely hydrogenated heteroaryl groups, e.g. furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl or pyrazolidinyl. Preferred heterocyclic groups are 5- or 6-membered heteroaryl groups and the most preferred heterocyclic group is a morpholinyl, thiomorpholinyl or piperidinyl group.

**[0020]** A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred S1P receptor agonist of formula III, which is the one used according to the invention as defined in claim 1, is FTY720, *i.e.* 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride, as shown:



**[0021]** For disclosure purposes, a preferred compound of formula II is the one wherein each of

R'<sub>2</sub> to R'<sub>5</sub> is H and m is 4, i.e. 2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g. the hydrochloride.

**[0022]** For disclosure purposes, a preferred compound of formula III is the one wherein W is CH<sub>3</sub>, each of R''<sub>1</sub> to R''<sub>3</sub> is H, Z<sub>2</sub> is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound C), e.g. the hydrochloride. The R-enantiomer is particularly preferred.

**[0023]** For disclosure purposes, a preferred compound of formula IVa is the FTY720-phosphate (R<sub>2a</sub> is H, R<sub>3a</sub> is OH, X<sub>a</sub> is O, R<sub>1a</sub> and R<sub>1b</sub> are OH). A preferred compound of formula IVb is the Compound C-phosphate (R<sub>2a</sub> is H, R<sub>3b</sub> is OH, X<sub>a</sub> is O, R<sub>1a</sub> and R<sub>1b</sub> are OH, Y<sub>a</sub> is O and R<sub>4a</sub> is heptyl). A preferred compound of formula V is Compound B-phosphate.

**[0024]** For disclosure purposes, a preferred compound of formula VII is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

**[0025]** For disclosure purposes, a preferred compound of formula Xa is e.g. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a prodrug thereof.

**[0026]** For disclosure purposes, it will be appreciated that the compounds as described herein may be the direct active substances, or may be prodrugs. For example, the compounds may be phosphorylated forms.

### ***Oral Formulations***

**[0027]** For disclosure purposes, the dosage form of a composition of the present invention, e.g. the final dosage form, may be a solid dosage form, e.g. a tablet. In another embodiment of the present invention the dosage form is granular, e.g. powder form and may comprise part of a suspension or gel. Another dosage forms may comprise of small multiparticulate pellets/beads. Other dosage forms may comprise a solid or granular composition which is soluble in a liquid to produce a liquid formulation prior to administration. Examples of such formulations are soluble tablets, capsules and sachets. The final liquid formulation may be consumed as a drink.

**[0028]** The oral route is often the most convenient route for drug administration. This may be in the form of a standard tablet, a conventional orally disintegrating tablet, a lyophilized tablet, or a thin film.

**[0029]** It has been found that compounds comprising a group of formula Y, e.g. amino-

propane-1,3-diols, e.g. those that have S1P agonist activity, are not easy to formulate. In particular, these are not easy to formulate in a solid oral formulation.

**[0030]** As such, the present inventors have surprisingly found that only a limited number of excipients are potentially feasible with such amino diols.

### ***The Maillard Reaction***

**[0031]** The Maillard reaction is a chemical reaction between an amino acid and a reducing sugar [Sugars that contain aldehyde groups that are oxidised to carboxylic acids are classified as reducing sugars.

**[0032]** Reducing sugars include glucose, glyceraldehyde, lactose, arabinose and maltose], usually requiring the addition of heat. Like caramelization, it is a form of non-enzymatic browning. The reactive carbonyl group of the sugar interacts with the nucleophilic amino group of the amino acid, and interesting but poorly characterized odor and flavor molecules result. This process accelerates in an alkaline environment because the amino groups do not neutralize. This reaction is the basis of the flavouring industry, since the type of amino acid determines the resulting flavour.

**[0033]** The potentially feasible excipients are classified into e.g. fillers, binders, disintegrants, lubricants, flow regulators, plastisizers, and matrix formers. Some excipients can be listed in more than one class.

**[0034]** Typical ranges found in a final formulation comprising a compound as described herein are as follows:

Fillers: 10 - 97 %

Binders: 1 - 15 %

Disintegrants: 1 - 15 %

Lubricants: 0.5 - 2 %

Flow regulators: 0.5 - 3 %

Matrix formers: 3 - 50 %

Plastisizers: 5 - 30 %

Flavoring agents: 1 - 20 %

Sweeteners: 1 - 20 %

**[0035]** Therefore, stable blends as defined in claim 1 or any one of the dependent claims consisting a compound having a group of formula Y which is FTY720 in free form or as a pharmaceutically acceptable salt thereof and one other excipient are disclosed.

**[0036]** The present invention relates to the use according to claim 1 or any one of the dependent claims of a binary blend consisting a compound having a group of formula Y as defined in claim 1 or a dependent claim thereof and one excipient selected from:  
Lactose, HPMC, croscarmellose sodium and starch, preferably an hydrous, whereby the binary blend is free from impurities.

**[0037]** Preferably, no moisture is present.

**[0038]** The formulation or blend for use according to the present invention does not comprise a reducing sugar, e.g glucose, glyceraldehyde, lactose, arabinose and maltose.

**[0039]** The formulation or blend for use according to the present invention does not comprise PEG, stearic acid,

**[0040]** The compositions used according to the present invention are binary blends, i.e. a mixture of a compound consisting a group of formula Y as defined in claim 1 or any one of its dependent claims and one excipient as listed in claim 1.

**[0041]** A particular advantage of the stable binary blends as disclosed herein is that they may be transported and stored prior to final formulation, without forming degradation products. The binary blends used according to the present invention therefore provide a commercially viable option for storing the S1P modulator as described herein in stable conditions.

**[0042]** Prior to the surprising findings of the present invention, the instability of the compounds comprising a group Y would not have been able to be safely stored, without the possibility of impurities being formed. With the present invention, the skilled person is now shown which excipients may be used with the S1P modulators for storage and, most importantly, which excipients may be used to reduce the risk of impurities contaminating a final drug product, such impurities being formed by a malliard reaction.

***Levels of impurities tolerated:***

**[0043]** Binary blends for use according to the present invention are free from impurities. It will be understood that the level of impurities tolerated will be judged using pharmaceutically acceptable standards.

**[0044]** However, it is also understood the pharmaceutical standards may only apply to a final dosage form, i.e. the final product. The present invention, in a preferred embodiment provides

for a use according to claim 1 or any one of the dependent claims of binary blends containing an S1P receptor modulator as defined herein, i.e. a compound comprising a group of formula Y as defined in claim 1 or any one of its dependent claims, which are free of impurities. The binary blends for use according to the present invention meet the following criteria for level of impurities:

- No more than 4.5wt% of impurities and/or but no more than 2wt% for an individual impurity.
- Preferably, impurities are at 2wt% or lower with no individual impurity being more than 0.5wt%

**[0045]** The "wt%" measurements above are indicators of amount of impurities tolerated. The term "wt%" means the percentage in relation to the amount of the whole formulation, for example 4wt% means 4mg in a 100mg tablet.

**Example of impurity tolerances, using the compound FTY720 as a reference**

**[0046]** There are three qualified degradation products observed in a dosage form: acetyl amide, palmitate amide and stearate amide.

**[0047]** The mechanism for the formation of these degradation products is postulated to be due to a nucleophilic attack of the primary amine of the FTY720 molecule at the carbonyl carbon of the acetic, palmitic or stearic acid.

**[0048]** Based on tox qualification study, the three primary degradation products, acetyl amide, palmitate amide and stearate amide were qualified at levels of 4.6%, 4.5% and 4.8%, respectively.

**[0049]** In order to adequately control the quality and efficacy of the final dosage product each qualified degradation product was assigned a specification of equal to or less than 2.0% of label strength.

**[0050]** The specified degradation products were assigned a specification of equal to or less than 1.0% of label strength.

**[0051]** The unspecified degradation products were assigned a specification of equal to or less than 0.5% of label strength as per the Novartis drug product purity policy.

**[0052]** The sum of all the degradation products above the limit of quantitation (0.1% label strength) was set at equal or less than a total of 4.5%.

***FTY720 as compound comprising a group of formula Y:***



**[0053]** A chemical stability program using binary mixtures of FTY720 and excipients (1 % drug substance was stored for 1 month in closed vials at 50°C) was performed using FTY720 drug substance.

**[0054]** General method to prepare binary mixtures:

1. 1. 10 mg drug substance and 1000 mg excipient were filled into a glass vial (= binary mixture).
2. 2. The closed vials were stored for 1 month at 50°C.

**[0055]** The analytical characterization was performed using gradient HPLC with UV detection. For the analysis, the stored samples were dissolved in 40 ml of 0.0005N hydrochloric acid in isopropanol and stirred with a magnetic stirrer for 30 minutes. This solution was centrifuged and an aliquot of the clear supernatant was used as the test solution.

**[0056]** The limit of quantitation (loq) of the method was 0.1 %. The rel. standard deviation  $s_{rel}$  of the assay determinations was  $\leq 2$  %.

Apparatus	HPLC system with gradient capability, autosampler and UV detector
Column	Waters Xterra™ MS C <sub>8</sub>
	Length 50 mm, internal diameter 4.6 mm, particle size 2.5 µm, Part number 186000603.

### Chromatographic conditions

**[0057]**

Mobile phase A	100 mM NaClO <sub>4</sub> buffer, pH 2.8:methanol = 93:7 (v/v)		
Mobile phase B	Acetonitrile		
Gradient program (linear)	Time [min.]	Phase A [%]	Phase B [%]
	0	70	30
	1.0	70	30
	15.0	58	42
	28.0	5	95
	30.0	5	95
	30.1	70	30

Gradient program (linear)	Time [min.]	Phase A [%]	Phase B [%]
	35.0	70	30
Flow rate	1.5 ml/min		
Detection	UV detection at 215 nm		
Column temperature	30°C		
Auto-sampler Temperature	Ambient		
Injection volume	10 µl		
Run time	35 min		

[0058] The tables below provide a list of potentially feasible excipients including the results of the stability program.

**Example 1: FTY720 stability test with selected fillers**

[0059]

Excipient	Assay in %	Σ impurities in %
Lactose anhydrous	101.4	0.0
Maize starch	102.2	0.0
Mannitol (for reference purposes only)	102.3	0.0
Mannitol granulated (SD 200) (for reference purposes only)	99.5	0.3
Avicel (for reference purposes only)	97.9	0.2
Citric acid + Mannitol (10+90) (for reference purposes only)	102.4	0.0
Sodium hydrogen carbonate + Mannitol (10+90) (for reference purposes only)	102.7	0.0

**Example 2: FTY720 stability test with selected binders**

[0060]

Excipient	Assay in %	Σ impurities in %
HPMC 3cPs	97.8	0.0
HP-Cellulose LH-22 (for reference purposes only)	99.8	0.4

Excipient	Assay in %	$\Sigma$ impurities in %
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**Example 3: FTY720 stability test with selected disintearants:****[0061]**

Excipient	Assay in %	$\Sigma$ impurities in %
Maize starch	102.2	0.0
Crosscarmellose sodium	102.4	0.0
Sodium carboxymethylstarch (Primojel) (for reference purposes only)	103.2	0.0
Starch 1500 (Sta RX)	101.3	0.0

**Example 4: FTY720 stability test with selected lubricants:****[0062]**

Excipient	Assay in %	$\Sigma$ impurities in %
Hydrogenated ricinoleic oil (Cutina) (for reference purposes only)	103.6	0.0
Mg stearate + Manitol (1+99) (for reference purposes only)	103.5	0.5

**Example 5: FTY720 stability test with selected flow regulators:****[0063]**

Excipient	Assay in %	$\Sigma$ impurities in %
Aerosil 200 (for reference purposes only)	101.5	0.6

**Example 6: FTY720 stability test with selected matrix formers:****[0064]**

Excipient	Assay in %	Σ impurities in %
Hydroxypropyl methyl cellulose	97.8	0.0
Hydroxypropyl cellulose (for reference purposes only)	99.8	0.4
Methyl cellulose (for reference purposes only)	-	-
Ethyl cellulose (for reference purposes only)	-	-
Pullulan (for reference purposes only)	-	-
Starch, e.g. Pure Cote	102.2	0.0
Povidone (for reference purposes only)	95.4	0.5

Polymers having different molecular weights may be used in the same formulation, e.g. having a low and a high molecular weight, i.e. one can use a mixture of e.g. cellulose type polymers having a low and a high MW to provide for different properties.

**Example 7: FTY720 stability test with selected plastisizers:**

[0065]

Excipient	Assay in %	Σ impurities in %
PEG 400 (for reference purposes only)	-	-
Dibutyl sebacate (for reference purposes only)	-	-
Sorbitol (for reference purposes only)	-	-

**Example 8: FTY720 stability test with selected flavoring agents:**

[0066]

Excipient	Assay in %	Σ impurities in %
Menthol (for reference purposes only)	-	-
Tutti frutti (for reference purposes only)		

**Example 9: FTY720 stability test with selected sweeteners:**

[0067]

Excipient	Assay in %	Σ impurities in %
Sucralose (for reference purposes only)	-	-
Sodium saccharine (for reference purposes only)	-	-

Excipient	Assay in %	$\Sigma$ impurities in %
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#### Example 10: Non-feasible excipients

[0068] An example of a non-feasible excipient is shown below. The method to prepare the binary mixtures and the analytical characterization are the same as describe before.

Excipient	Assay in %	$\Sigma$ impurities in %
Glycerylbehenat (Compritol)	96.2	> 2

#### Reference-Example 10: S1P Assays

[0069] The binding affinity of S1P receptor modulators to individual human S1P receptors may be determined in following assay:

S1P receptor modulator activities of compounds are tested on the human S1P receptors S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub>. Functional receptor activation is assessed by quantifying compound induced GTP [ $\gamma$ -<sup>35</sup>S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA- bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20 $\mu$ g/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 10  $\mu$ M GDP, 0.1% fat free BSA and 0.2 nM GTP [ $\gamma$ -<sup>35</sup>S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [ $\gamma$ -<sup>35</sup>S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [ $\gamma$ -<sup>35</sup>S] is quantified with a TOPcount plate reader (Packard). EC<sub>50</sub>s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators preferably have a binding affinity to S1P receptor <50 nM.

[0070] Preferred S1P receptor modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Naive cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

[0071] The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

A S1P receptor modulator or the vehicle is administered orally by gavage to rats. Tail blood for

hematological monitoring is obtained on day -1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

**Final Product Manufacture:**

**[0072]** The manufacture of final pharmaceutical products may be carried out using conventional techniques. Examples of such techniques are described below, by way of example.

**Compressed tablets**

**[0073]** Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogeneous mix of components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to ensure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation.

**[0074]** Powders that can be mixed well and therefore do not require granulation can be compressed in to a tablet through a technique called Direct Compression.

**Lyophilised Tablets**

**[0075]** These tablets may be manufactured by way of creating a suspension containing the active ingredient and other excipients, for example Gelatin in an amount, for example, of about 3wt%, structure forming agents, such as mannitol or sorbitol, for example and in an amount, for example, of about 1.5wt%, sweeteners and flavouring agents.

**[0076]** A reference example of a lyophilised tablet formulation is provided below:

The Gelatin/Mannitol solution is cooled to 23°C and mixed with the active substance. The total solid content is preferably less than 50%. The suspension is then cooled to 15°C to prevent sedimentation of the suspension before the start of lyophilisation.

**Thin Films**

**[0077]** The binary blends of the present invention may be further mixed with additional excipients to form final products. The final products may be made from the binary compositions using standard techniques, such as the ones below:

Possible manufacturing comprises casting, drawing, extrusion or coating/lamination processes: Casting is a manufacturing process by which the drug/excipient mixture is introduced into a mold, allowed to solidify within the mold, and then ejected or broken out to make the individual thin film.

**[0078]** Drawing produces a roll by pulling on a molten drug/excipient mixture until it increases in length. This is typically accompanied by a thinning out of the material. The single units are then cut or punched out of these roles and packed, e.g. into pouches.

**[0079]** Extrusion creates rolls by pushing and/or drawing through a die of the desired profile shape. Extrusion may be continuous (producing indefinitely long material) or semi-continuous (producing many short pieces). The single units are then cut or punched out of these roles and packed, e.g. into pouches.

**[0080]** Coating/lamination could be described as manufacturing a laminate first by coating and lamination. The resulting roll is then splitted into smaller rolls. The single units are then cut or punched out of these roles and packed, e.g. into pouches.

**[0081]** According to the invention, the final dosage forms obtained according to the present invention are useful for:

1. a) treatment and prevention of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, and the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation; particularly in the treatment of acute or chronic allo- and xenograft rejection or in the transplantation of insulin producing cells, e.g. pancreatic islet cells;
2. b) treatment and prevention of autoimmune disease or of inflammatory conditions, e.g. multiple sclerosis, arthritis (for example rheumatoid arthritis), inflammatory bowel disease, hepatitis, etc.;
3. c) treatment and prevention of viral myocarditis and viral diseases caused by viral myocarditis, including hepatitis and AIDS.
4. d) treatment and prevention of cancer, e.g. solid tumors, carcinoma, e.g. for preventing metastatic spread of tumours or for preventing or inhibiting growth of micrometastasis

**[0082]** By "solid tumors" are meant tumors and/or metastasis (wherever located) other than lymphatic cancer, e.g. brain and other central nervous system tumors (eg. tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastomas); head and/or neck cancer; breast tumors; circulatory system tumors (e.g. heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (e.g. kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (e.g. oesophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus

and anal canal), tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of biliary tract, pancreas, other and digestive organs); oral cavity (lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (e.g. vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male genital organs); respiratory tract tumors (e.g. nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, e.g. small cell lung cancer or non-small cell lung cancer); skeletal system tumors (e.g. bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (e.g. malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites. Where hereinbefore and subsequently a tumor, a tumor disease, a carcinoma or a cancer is mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis is.

## REFERENCES CITED IN THE DESCRIPTION

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## Patentkrav

1.       Anvendelse af en binær blanding, der består af:
  - (i) 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol (FTY720) i fri form eller som et  
5 farmaceutisk acceptabelt salt deraf og
  - (ii) ét hjælpestof valgt fra gruppen, der består af:  
lactose, hydroxypropylmethylcellulose (HPMC), croscarmellose-natrium og stivelse,  
til fremstilling af et medikament til anvendelse til behandling af organ- eller  
vævstransplantatafstødning, graft-versus-host-sygdom, autoimmunsygdomme,  
10 inflammatoriske tilstande, viral myocarditis og virussygdomme forårsaget af viral  
myocarditis eller cancere, hvor den binære blanding er fri for urenheder.
  
2.       Anvendelse ifølge krav 1, hvor den binære blanding består af 2-amino-2-[2-(4-  
octylphenyl)ethyl]propan-1,3-diol (FTY720) i fri form eller som et farmaceutisk  
15 acceptabelt salt deraf og af lactose.
  
3.       Anvendelse ifølge krav 1, hvor den binære blanding består af 2-amino-2-[2-(4-  
octylphenyl)ethyl]propan-1,3-diol (FTY720) i fri form eller som et farmaceutisk  
acceptabelt salt deraf og af HPMC.  
20
  
4.       Anvendelse ifølge krav 1, hvor den binære blanding består af 2-amino-2-[2-(4-  
octylphenyl)ethyl]propan-1,3-diol (FTY720) i fri form eller som et farmaceutisk  
acceptabelt salt deraf og af croscarmellose-natrium.
  
- 25 5.       Anvendelse ifølge krav 1, hvor den binære blanding består af 2-amino-2-[2-(4-  
octylphenyl)ethyl]propan-1,3-diol (FTY720) i fri form eller som et farmaceutisk  
acceptabelt salt deraf og af stivelse.