Claims

1. A compound of the general formula (I):

P-E-I (I)

or a pharmaceutically acceptable salt thereof, wherein

P is a group represented by the general formula (II):

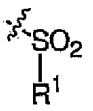
$$-(CH_2)_n-O-(CH_2)_k-X \qquad (II)$$

wherein

n is an integer of from 3 to 8; and

k is 0, 1 or 2; most preferably k is 1;

X represents CH_2OH, CH_2OAc, CH(O) or a group selected from the group consisting of: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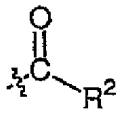
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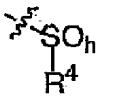
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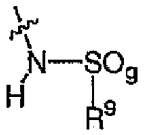
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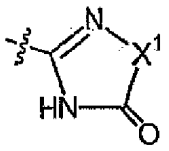
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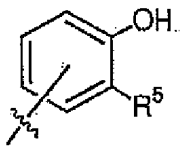
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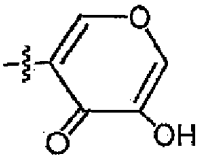
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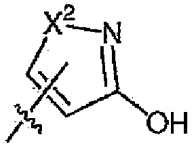
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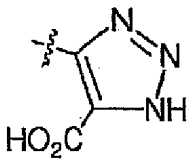
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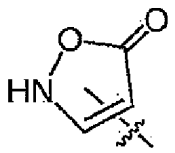
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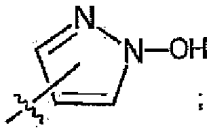
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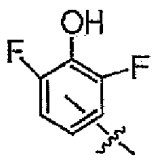
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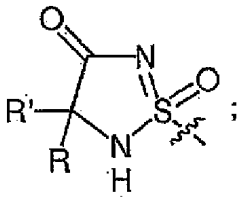
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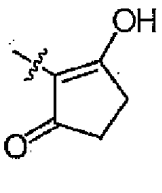
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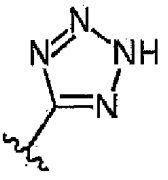
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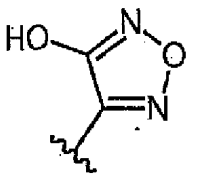
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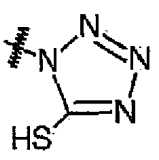
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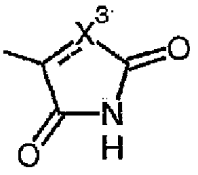
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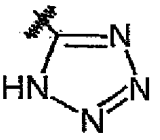
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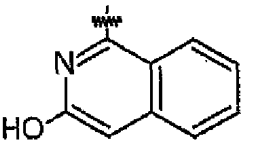
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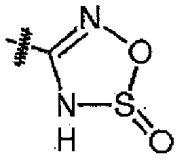
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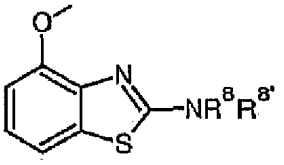
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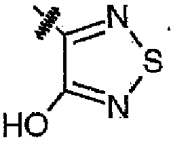
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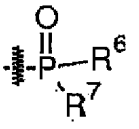
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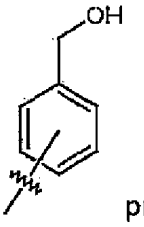
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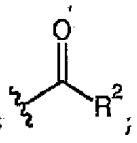
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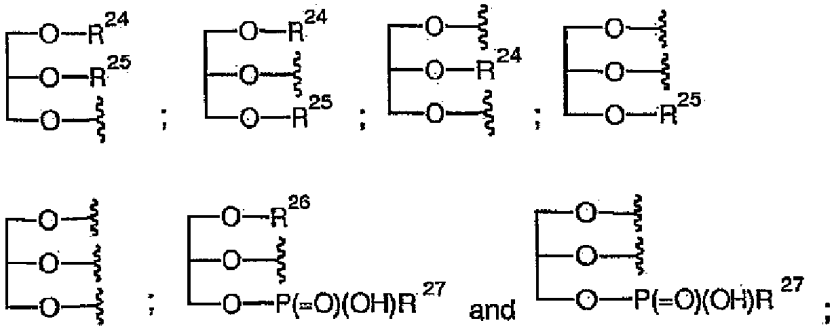
wherein

R and R^1 each independently represents a hydrogen atom; or a C_1-C_6alkyl group which may be substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s);

R^1 represents a hydroxyl group, C_1-C_6alkoxy, —NHCN, —NH(C_1-C_6alkyl), —NH(C_3-C_6cycloalkyl), —NH(aryl), or —O(C_1-C_6alkyldiyl)O(C=O)R^{11}; R^{11} is a C_1-C_6alkyl group which is optionally substituted with one or more fluorine or chlorine atom(s); or a C_3-C_6cycloalkyl group which is optionally substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s);

R^2 represents -NHR^3; -$NR^{20}R^{21}$; -OR^{22}; -$\{OCH_2$-$CH_2\}_l$-R^{23}; -C_3-C_{10}-heterocyclyl optionally substituted with one, two or three substituents independently selected from the group consisting of hydroxyl group, C_1-C_6alkoxy, C_1-C_6alkyl, and oxo; -$\{Xaa\}_o$; a mono-, or disaccharide, or a derivative thereof, which is joined to -C(O) by an ester bond via the 1-O-, 3-O-, or 6-O-position of the saccharide;

or is selected from the group consisting of:



wherein

R^3 represents (SO_2R^{30}); (OR^{31}); -C_1-C_6alkanediyl(SO_2R^{32}); -C_1-C_6alkanediyl(CO_2H), an aryl group, a heteroaryl group, a cycloalkyl group or a heterocycloalkyl group, wherein the aryl group is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl, and -C(=O)OR^{51}; wherein the heteroaryl group, is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl and -C(=O)OR^{51}; where the cycloalkyl group is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl),—N(C_1-C_6)dialkyl, and -C(=O)OR^{51} ; and wherein the heterocycloalkyl group is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl),—N(C_1-C_6)dialkyl and -C(=O)OR^{51};

R^{30} is a C_1-C_6alkyl, or an aryl group, wherein the C_1-C_6alkyl group is optionally substituted with -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, one, two or three fluorine or chlorine atoms, or a hydroxyl group; and wherein the aryl group is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), and —N(C_1-C_6)dialkyl;

R^{31} is a C_1-C_6alkyl group which is optionally substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s); or a C_3-C_6cycloalkyl group which is optionally substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s);

R^{32} is a C_1-C_6alkyl group which is optionally substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s); or a C_3-C_6cycloalkyl group which is optionally substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s);

R^{20} and R^{21} each independently represents a hydrogen atom; a C_1-C_6alkyl group which may be substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s); a C_3-C_6cycloalkyl group which may be substituted with one or more fluorine or chlorine atom(s) or hydroxyl group(s); -C_1-C_6alkyldiyl(CO_2H) or together form a C_3-C_{10}-heterocycloalkyl which may be substituted with one or more C_1-C_6alkyl group(s), C_1-C_6alkoxy group(s), fluorine or chlorine atom(s) or hydroxyl group(s);

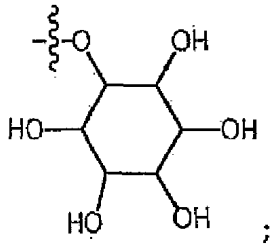
R^{22} is a hydrogen atom, a C_1-C_6alkyl group; or a C_3-C_6cycloalkyl group; wherein the C_1-C_6alkyl group or the C_3-C_6cycloalkyl group is optionally substituted with -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, —NH(C_1-C_6)alkyldiyl- C_1-C_6alkoxy, one, two or three fluorine or chlorine atom(s), hydroxyl, or C_1-C_6alkoxy, an aralkyl group, a heteroalkyl group or a heteroalkylcycloalkyl group;

R^{23} is -OH, -O(C_1-C_3)alkyl, or -N(C_1-C_3)dialkyl;

i is an integer of from 1 to 10;

R^{24}, R^{25}, and R^{26} each independently represents a hydrogen atom; —C(=O)C_{11}-C_{21}alkyl; or —C(=O)C_{11}-C_{21}alkenyl;

R^{27} represents —OH; —O(CH_2)$_2NH_2$, —OCH_2-[CH(NH_2)(CO_2H)], —O(CH_2)$_2$N(CH_3)$_3$; or



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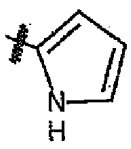
Xaa represents Gly, a conventional D,L-, D- or L-amino acid, a non-conventional D,L-, D- or L-amino acid, or a 2- to 10-mer peptide; and is joined to -C(=O) by an amide bond;

o is an integer of from 1 to 10;

R^4 is selected from the group consisting of: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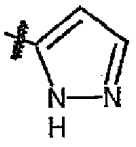
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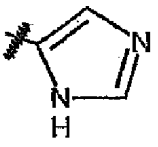
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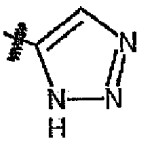
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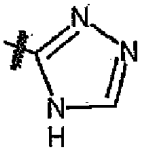
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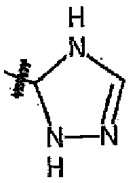
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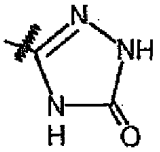
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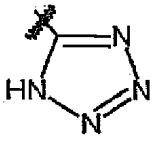
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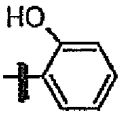
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h is 0, 1, or 2;

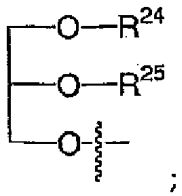
R^5 represents a hydrogen atom; a fluorine or chlorine atom; $-CF_3$; $-C(=O)OR^{51}$; $-NHC(=O)R^{52}$; $-C(=O)NR^{53}R^{54}$; or $-S(O_2)OH$;

R^{51} represents a hydrogen atom; a C_1-C_6alkyl group; or a C_3-C_6cycloalkyl group; wherein the C_1-C_6alkyl group or the C_3-C_6cycloalkyl group is optionally substituted with $-NH_2$, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, —NH(C_1-C_6)alkyldiyl-C_1-C_6alkoxy, one, two or three fluorine or chlorine atom(s), hydroxyl, or C_1-C_6alkoxy;

R^{52}, R^{53} and R^{54} each independently represents a C_1-C_6alkyl group which is optionally substituted with one or more fluorine or chlorine atom(s); a C_3-C_6cycloalkyl group which is optionally substituted with one or more fluorine or chlorine atom(s); or an aryl group which is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl, and an oxo substituent;

R^6 and R^7 each independently represents a hydroxyl group; an -O(C_1-C_6)alkyl group, an -O(C_2-C_6)alkenyl group, a, -O(C_1-C_6)alkyldiylO(C=O)(C_1-C_6)alkyl group, or a -O(C_1-C_6)alkyldiylO(C=O)(C_2-C_6)alkenyl group; wherein the C_1-C_6alkyl group and the C_2-C_6alkenyl group may be substituted with NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6 alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, or one, two or three fluorine or chlorine atom(s); or

R^6 represents a hydroxyl group and R^7 represents a group:



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R^9 represents C_1-C_6alkyl, or aryl; wherein the C_1-C_6alkyl is optionally substituted with -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, —NH(C_1-C_6)alkyldiyl-C_1-C_6alkoxy, one, two or three fluorine or chlorine atom(s), hydroxy, C_1-C_6alkoxy, aryl, aryloxy, —C(=O)-aryl, —C(=O)C_1-C_6alkoxy; and wherein the aryl group is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl, and an oxo substituent;

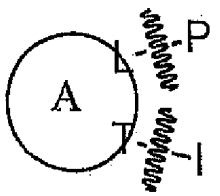
g is 1 or 2;

X^1 represents an oxygen atom; sulfur atom; or NH;

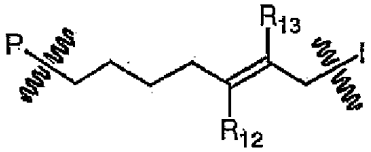
X^2 represents an oxygen atom; sulfur atom; NH; or N(CH_3);

X^3 represents an oxygen atom; sulfur atom; nitrogen atom; carbon atom; or C-OH; and the dashed line represents a carbon-carbon bond or a carbon-carbon double bond;

E is a group represented by the general formula (III) or (IV):



(III)



(IV)

wherein R12 and R13 are preferably in cis configuration, and wherein

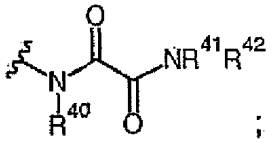
ring A in formula (III) represents a 5-membered or 6-membered carbocyclic or heterocyclic ring containing at least one double bond, including an aromatic carbocyclic or heterocyclic ring, which can be substituted with one to three or one to four substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), and —N(C_1-C_6)dialkyl; and L and T each independently represents a ring atom, wherein L and T are adjacent to another;

R^{12} and R^{13} each independently represents a hydrogen atom, a fluorine atom, hydroxyl, -NH_2, C_1-C_6alkyl, C_1-C_6alkoxy, —C(=O)-aryl, —C(=O)C_1-C_6alkyl, or -SO_2(C_1-C_6alkyl); or -SO_2aryl; wherein any of the foregoing C_1-C_6alkyl, C_1-C_6alkoxy, or aryl are optionally substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, fluorine or chlorine atom, and hydroxyl; or R^{12} and R^{13} are taken together to form a 5-membered or 6-membered ring, which ring is optionally substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, fluorine or chlorine atom, and hydroxyl;

L is –$(CH_2)_m$-Y, wherein

m is an integer of from 3 to 6, provided that m is an integer of from 3 to 5 when E is a group according to general formula (III);

Y represents a group selected from the group consisting of:


(oxamide)

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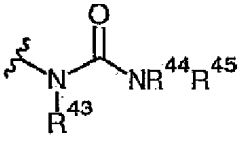

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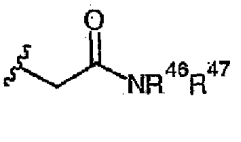

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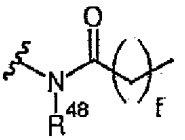

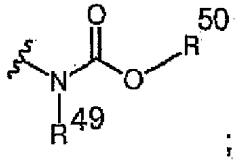

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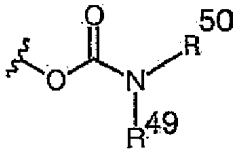


wherein

R^{40}, R^{41}, R^{43}, R^{44}, R^{46}, R^{48} and R^{49} each independently represents a hydrogen atom, -C_1-C_6alkyl, -C_3-C_6cycloalkyl, -C_1-C_6alkoxy, —C(=O)aryl, or —C(=O)C_1-C_6alkyl, wherein any of the foregoing C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkoxy, or aryl are optionally substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-

C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, fluorine or chlorine atom, and hydroxy; or R^{40} and R^{41}, or R^{43} and R^{44}, are taken together to form a 5-membered or 6-membered ring, which ring may be substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, fluorine or chlorine atom, and hydroxyl;

R^{42}, R^{45}, R^{47} and R^{50} each independently represents a -C_1-C_3alkyl, wherein the C_1-C_3alkyl may be substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_3)alkyl, —N(C_1-C_3)dialkyl, C_1-C_3alkylcarbonyloxy-, C_1-C_3alkoxycarbonyloxy-, C_1-C_3alkylcarbonylthio-, C_1-C_3alkylaminocarbonyl-, di(C_1-C_3)alkyl-aminocarbonyl-, fluorine or chlorine atom, and hydroxyl; or R^{40} and R^{41}; R^{43} and R^{44}; R^{49} and R^{50} are taken together to form a 5-membered or 6-membered ring, which ring may be substituted with one, two or three substituents independently selected from the group consisting of -NH_2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, C_1-C_6alkylcarbonyloxy-, C_1-C_6alkoxycarbonyloxy-, C_1-C_6alkylcarbonylthio-, C_1-C_6alkylaminocarbonyl-, di(C_1-C_6)alkylaminocarbonyl-, fluorine or chlorine atom, and hydroxyl;

f is an integer of from 0 to 2;

with the proviso that

when X does not comprise a -C(=O)O-motif with the carbonyl carbon in *alpha* or *beta* position to the oxygen atom of general formula (II), Y is an oxamide, a carbamate or a carbamide, preferably Y is an oxamide as defined above.

2. The compound according to claim 1,

with the further proviso that

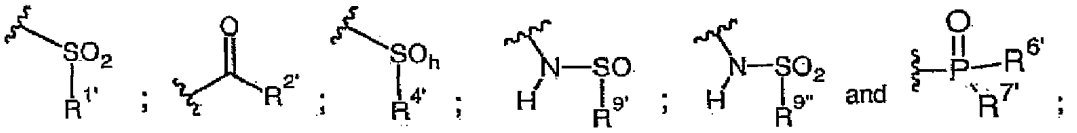
when n is 3, 5, 6, 7 or 8, k is 1 and E is a group according to general formula (III) or general formula (IV), wherein each of R^{12} and R^{13} is a hydrogen atom;

P represents a group:

$$-(CH_2)_3\text{-}O\text{-}(CH_2)\text{-}X^{81};\ -(CH_2)_5\text{-}O\text{-}(CH_2)\text{-}X^{81};$$

wherein

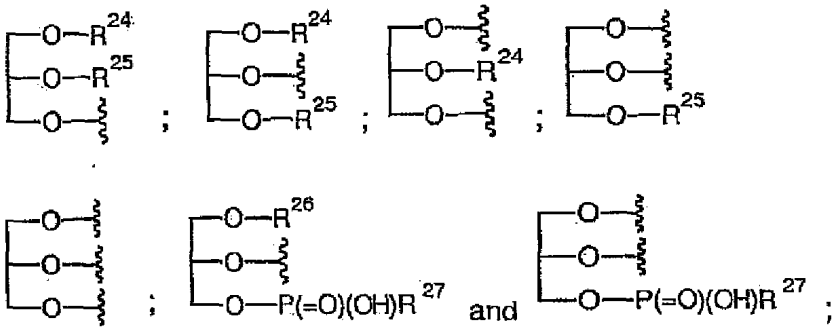
X^{81} represents a group selected from the group consisting of:



$R^{1'}$ is defined as R^1 above;

$R^{2'}$ represents -$NHR^{3'}$; -$OR^{22'}$; -$(OCH_2\text{-}CH_2)_i\text{-}R^{23}$; a mono-, or disaccharide, or a derivative thereof, which is joined to -C(=O) by an ester bond via the 1-O-, 3-O-, or 6-O-position of the saccharide;

or wherein R^2 is selected from the group consisting of:



wherein

$R^{3'}$ represents (SO_2R^{30}); (OR^{31}); -C_1-C_6alkanediyl(SO_2R^{32}); or -C_2-C_6alkanediyl(CO_2H);

$R^{22'}$ is a hydrogen or a C_3-C_6cycloalkyl group, which is optionally substituted with -NH2, —NH(C_1-C_6)alkyl, —N(C_1-C_6)dialkyl, —NH(C_1-C_6)alkyldiyl- C_1-C_6alkoxy, one, two or three fluorine or chlorine atom(s), hydroxy, or C_1-C_6alkoxy;

R^{23} and i are as defined above;

R^{24}, R^{25}, R^{26}, and R^{27} are as defined above;

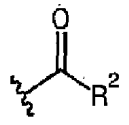
$R^{4'}$ is defined as R^4 above; and h is defined as above;

$R^{6'}$ and $R^{7'}$ are defined as R^6 and R^7 above;

$R^{8''}$ and $R^{8'''}$ are defined as R^8 and $R^{8'}$ above;

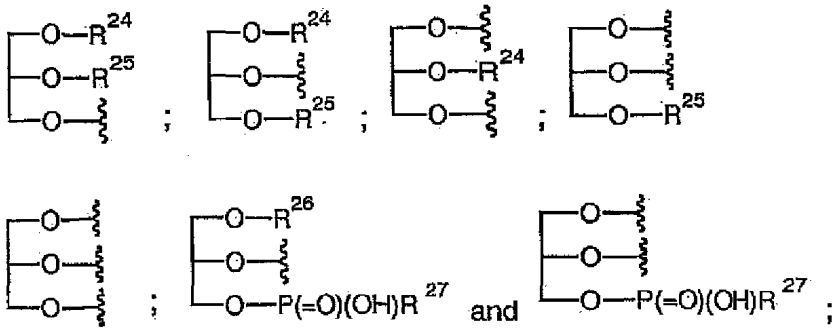
$R^{9'}$ is defined as R^9 above; $R^{9''}$ represents aryl which is optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl, and an oxo substituent.

3. The compound according to claim 1 or 2, wherein X is



wherein R^2 is $-OR^{22}$; $-(OCH_2-CH_2)_i-R^{23}$; a mono-, or disaccharide, or a derivative thereof, which is joined to -C(=O) by an ester bond via the 1-O-, 3-O-, or 6-O-position of the saccharide;

or wherein R^2 is selected from the group consisting of:



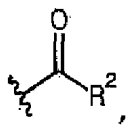
wherein R^{23} and i are as defined above;

and wherein R^{22}, and R^{23} to R^{27} are as defined in claim 1.

4. The compound according to any of claims 1 to 3, wherein X is -C(=O)OH or a suitable salt of the carboxylic acid, preferably a free carboxylic acid.

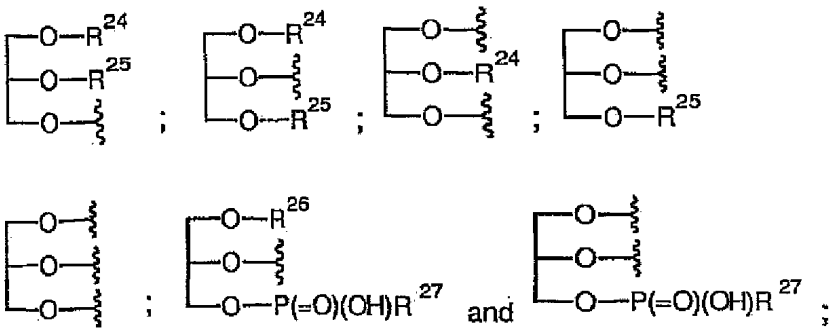
5. The compound according to any of claims 1 to 4, wherein Y is one of the oxamides defined according to claim 1.

6. The compound according to any of claims 1 to 3 and 5, wherein X is



wherein R^2 is $-OR^{22}$; $-(OCH_2-CH_2)_i-R^{23}$; a mono-, or disaccharide, or a derivative thereof, which is joined to -C(=O) by an ester bond via the 1-O-, 3-O-, or 6-O-position of the saccharide;

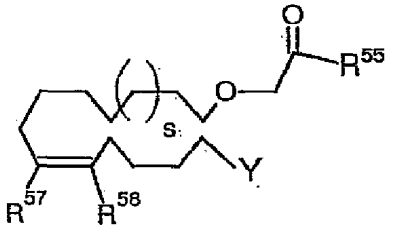
or wherein R^2 is selected from the group consisting of:



wherein and R^{22}, R^{23} to R^{27} and i are as defined in claim 1, and wherein Y is one of the oxamides defined according to claim 1.

7. The compound according to any of claims 1 to 6, wherein X is C(=O)OH, preferably the free carboxylic acid, and Y is one of the oxamides defined according to claim 1.

8. The compound according to claim 1, with the formula (V):



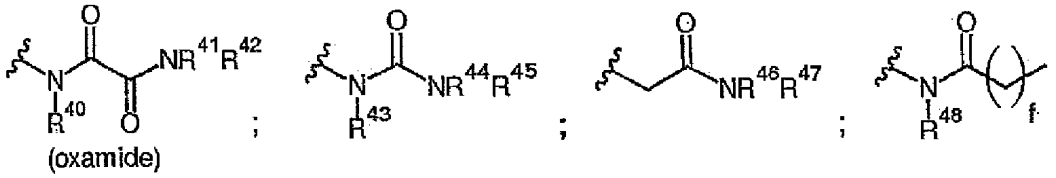
formula (V)

wherein

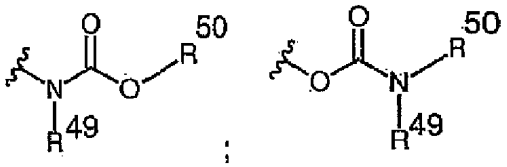
R^{55} represents -OH; $-OR^{22}$; $-(OCH_2-CH_2)_l-R^{23}$; a mono-, or disaccharide, or a derivative thereof, which is joined to -C(=O) by an ester bond via the 1-O-, 3-O-, or 6-O-position of the saccharide;

R^{22}, R^{23} and i are as defined in claim 1, preferably R^{22} is a hydrogen atom or a C_1-C_6alkyl group, more preferably a hydrogen atom and i is preferably 2 to 4, more preferably 3;

Y represents a group selected from the group consisting of:



(oxamide)



wherein R^{40} to R^{50} are defined in claim 1, preferably R^{40} is a hydrogen atom or a C_1-C_6alkyl group, more preferably a hydrogen atom

R^{57} and R^{58} are hydrogen; or form together a five- or six-membered ring, preferably an aromatic ring, optionally substituted with one to three or one to four substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, fluorine or chlorine atom, hydroxyl group, amino group, —NH(C_1-C_6alkyl), —N(C_1-C_6)dialkyl, and an oxo substituent;

s is 0, 1 or 2, with the proviso that s is 0 if R^{57} and R^{58} form together a five- or six-membered ring;

the double bond in formula (V) represents a double carbon-carbon bond in *cis*-configuration, if R^{57} and R^{58} are hydrogen, or this double bond is part of a five- or six-membered ring formed together by R^{57} and R^{58}.

9. The compound according to claim 8, wherein

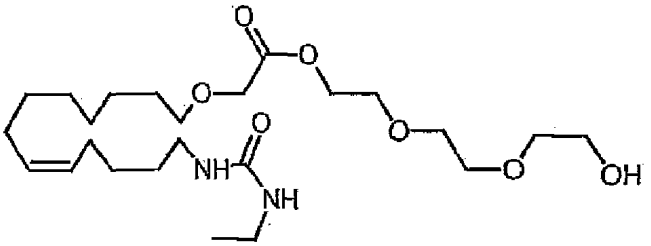
R^{55} represents –OH or-$(OCH_2$-$CH_2)_i$-R^{23}; i is 2 to 4, preferably i is 3; R^{23} is preferably OH;

Y is an oxamide, a carbamide or a carbamate, preferably a C_1-C_6alkyl substituted oxamide, carbamide or carbamate;

R^{57} and R^{58} are both H, or together form a substituted or non-substituted five- or six-membered aromatic ring, preferably form a substituted or non-substituted benzyl ring; and

s is 1 or s is 0 if R^{57} and R^{58} together form a substituted or non-substituted five- or six-membered aromatic ring.

10. The compounds according to any of claims 1 to 3, wherein the compound is selected from the group consisting of: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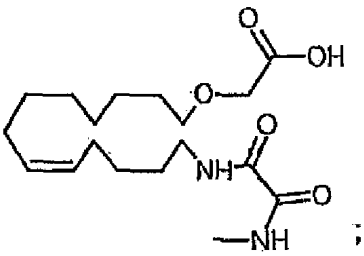
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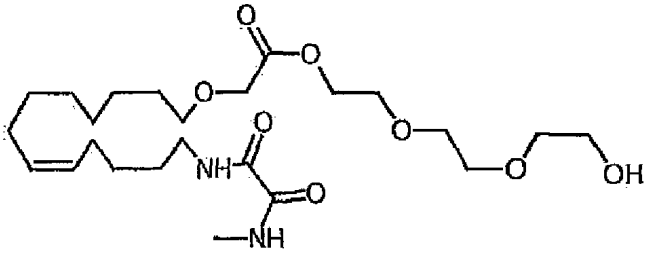
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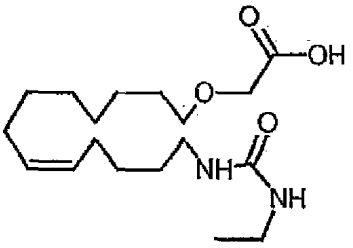
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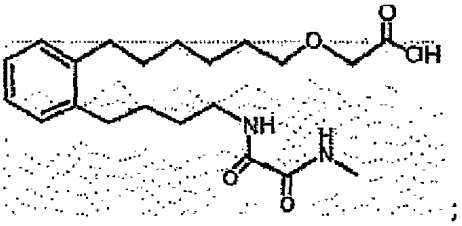
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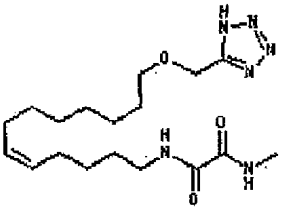
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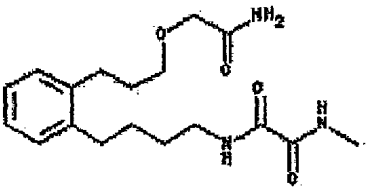
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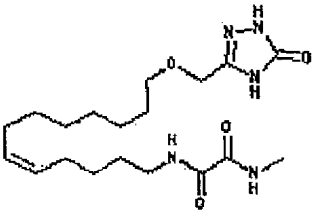
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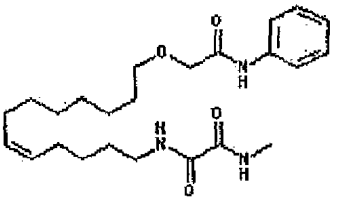
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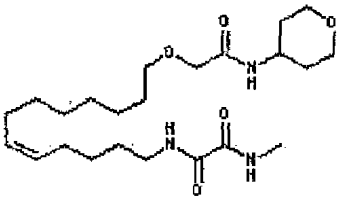
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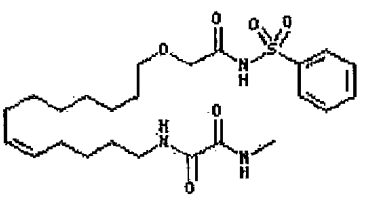
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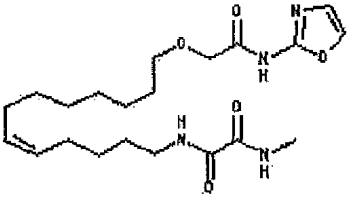
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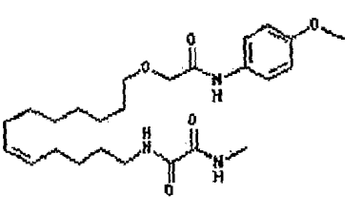
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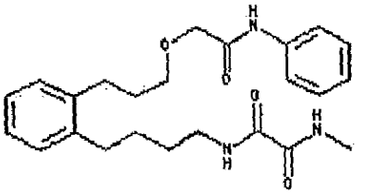
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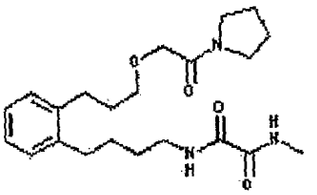
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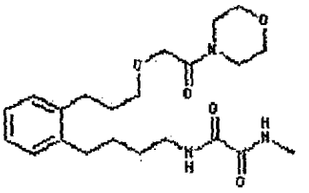
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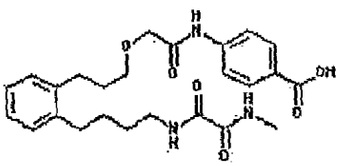
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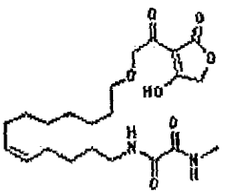
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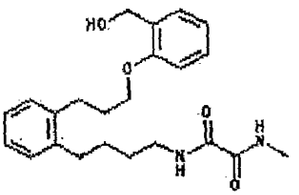
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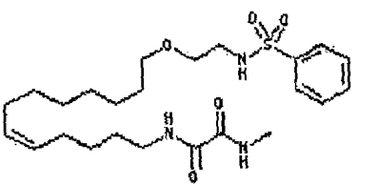
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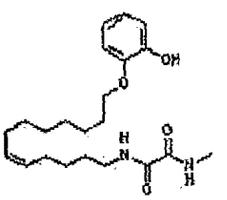
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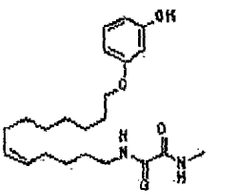
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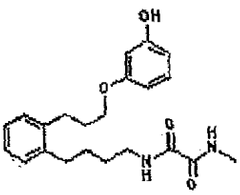
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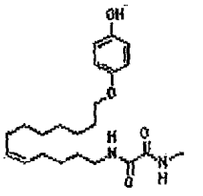
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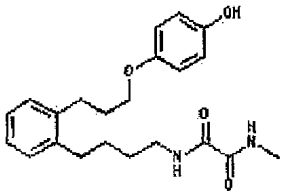
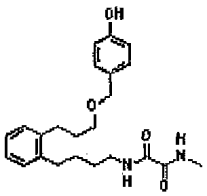
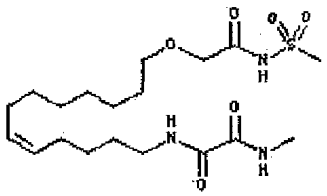
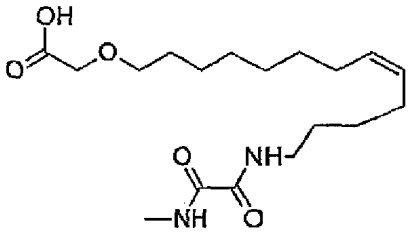
 ;  ;



or a pharmaceutically acceptable salt thereof.

11. The compound according to any of claims 1 to 10, with the formula (VI)



formula (VI)

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising the compound according to any of claims 1 to 11 in combination with a physiologically acceptable excipient.

13. The compound according to any of claims 1 to 11 or the pharmaceutical composition according to claim 12 for use in therapy.

14. Use of the compound according to any of claims 1 to 11 or the pharmaceutical composition according to claim 12 in the manufacture of a medicament for treating of cardiovascular diseases, preferably selected from the group consisting of atrial fibrillation, ventricular arrhythmia, heart failure, coronary artery disease, myocardial infarction, maladaptive cardiac

hypertrophy, and cardiac arrhythmias including ventricular extrasystoles, ventricular tachycardia, malignant ventricular tachycardia, atrial tachycardia, atrial flutter and atrial fibrillation, dilatative cardiomyopathy, and hypertensive heart disease, preferably selected from the group consisting of atrial fibrillation, atrial tachycardia, ventricular arrhythmia, heart failure.

15. The composition according to claim 12 or the use of the compound or composition according to claim 14, wherein the compound or composition is to be administered orally, topically, subcutaneously, intramuscularly, intraperitoneally, intravenously, intranasally, preferably orally or intraveneously, more preferably orally.

16. The use of the compound or composition according to any of claims 13 to 14, wherein the compound or composition is a dosage form selected from the group consisting of a spray, an aerosol, a foam, an inhalant, a powder, a tablet, a capsule, a soft gelatin capsule, a tea, a syrup, a granule, a chewable tablet, a salve, a cream, a gel, a suppository, a lozenge, a liposome composition and a solution suitable for injection.