

Aromatic di-keto derivatives, processes for their production and their use as a pharmaceutical.

5 The present invention relates to new aromatic di-keto derivatives and to their pharmaceutically acceptable salts, esters, ethers and other obvious chemical equivalents. The derivatives are glucose-6-phosphate translocase inhibitors and can be used in the treatment of diabetes mellitus. The present invention further relates to a process for the production of the derivatives, to the use of the derivatives and their
10 pharmaceutically acceptable salts, esters, ethers and other obvious chemical equivalents as pharmaceuticals, in particular to their use in the treatment of diabetes mellitus, and to pharmaceutical compositions comprising the derivatives, pharmaceutically acceptable salts, esters, ethers or other obvious chemical equivalents thereof.

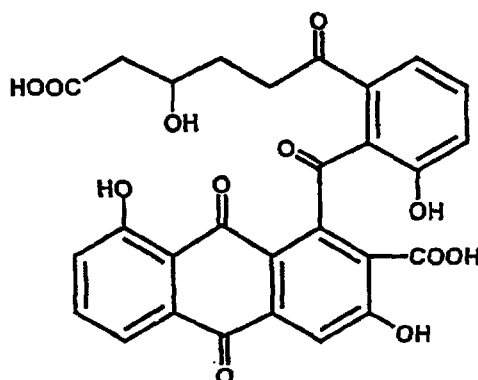
15 Increased rate of hepatic glucose output is a general feature of diabetes mellitus. In particular, there is a strong correlation between fasting plasma glucose level in non-insulin dependent diabetes mellitus (NIDDM) and hepatic glucose output. The two pathways by which glucose is produced in the liver are gluconeogenesis and
20 glycogenolysis. The terminal steps of both pathways is catalysed by the microsomal glucose-6-phosphatase, a key enzyme in the homeostatic regulation of blood glucose levels. The level of this enzyme has also been known to be elevated in both experimental and pathological conditions of diabetes. Interference with this enzyme system should, therefore, result in a reduced hepatic glucose production.

25 Hepatic glucose-6-phosphatase is a multicomponent system comprised of at least three functional activities: a glucose-6-phosphate translocase (T1), a glucose-6-phosphate phosphohydrolase and a phosphate/pyrophosphate translocase (T2). The glucose-6-phosphate translocase facilitates transport of glucose-6-phosphate into the lumen of the
30 endoplasmic reticulum (ER). The phosphohydrolase, with its active site situated on the luminal surface of the ER, hydrolyses glucose-6-phosphate and releases glucose and phosphate into the lumen. While the efflux of phosphate is facilitated by the phosphate/pyrophosphate translocase, the exact mechanism of glucose efflux is still not clear.

The high degree of substrate specificity of glucose-6-phosphate translocase makes this a potential target for pharmacological intervention in the treatment of diabetes mellitus. Thus, amongst physiologically occurring sugar phosphates, only glucose-6-phosphate is transported by the translocase. In contrast, the phosphatase is non-specific and is known to hydrolyse a variety of organic phosphate esters.

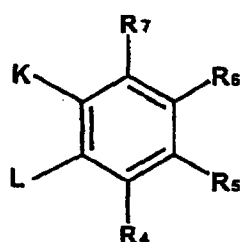
A series of non-specific inhibitors of glucose-6-phosphatase has been described in the literature, e.g. phlorrhizin (J. Biol. Chem. 242, 1955-1960 (1967)), 5,5'-dithio-bis-2-nitrobenzoic acid (Biochem. Biophys. Res. Commun. 48, 694-699 (1972)), 2,2'-diisothiocyanatostilbene and 2-isothiocyanato-2'-acetoxystilbene (J. Biol. Chem. 255, 1113-1119 (1980)). The first therapeutically utilizable inhibitors of the glucose-6-phosphatase system are proposed in EP-A-587 087 and EP-A-587 088. Kodaistatins A, B, C, and D described in PCT/EP 98/02247 are the first glucose-6-phosphate translocase inhibitors from microbial sources.

The aromatic di-keto derivatives according to the present invention may be derived from a compound named mumbaistatin. Mumbaistatin is described in PCT/EP99/04127. It is a natural product obtainable by cultivation of the microorganism *Streptomyces litmocidini*, a sample of which has been deposited on July 4, 1997, with the German Collection of Microorganisms and Cell Cultures (DSMZ) under the accession no. DSM 11641. The structural formula of mumbaistatin has now been determined and is given below:



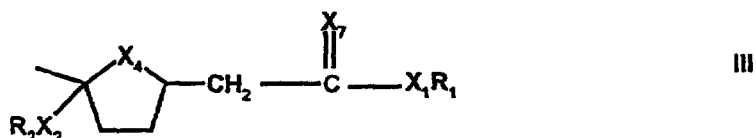
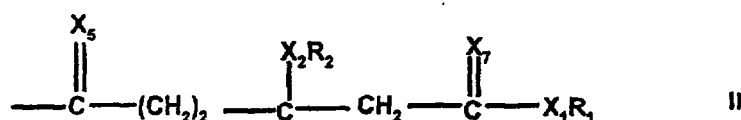
It has been found that certain derivatives of mumbaistatin have improved activity and are better tolerated in the mammalian body than mumbaistatin itself. Also, the separated diastereomers of mumbaistatin have advantages over the mumbaistatin mixture of diastereomers.

The present invention accordingly provides compounds of the general formula

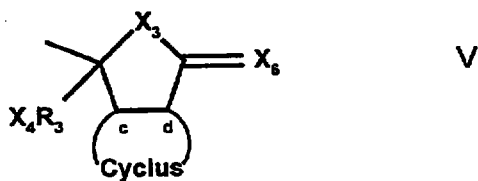
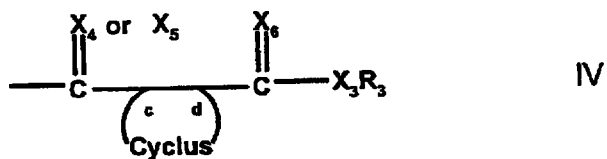


wherein

R₄, R₅, R₆ and R₇ are independently H, OH, halogen, optionally substituted alkyl, aryl or acyl, X-alkyl or X-aryl, where X is O, NH, N-alkyl or S, K is a group of the formula II or III below:



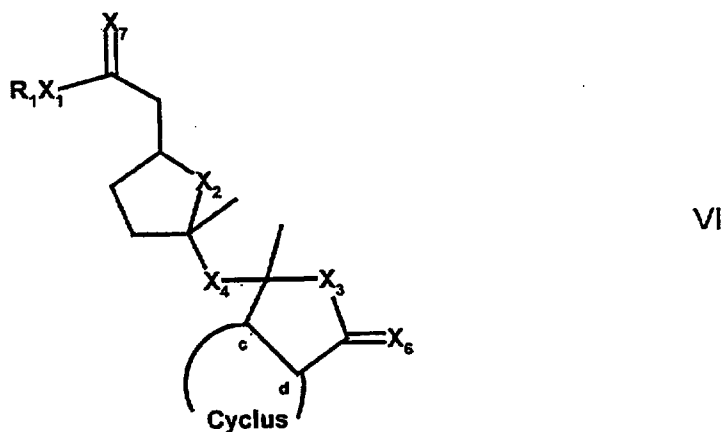
L is a group of the formula IV or V below:

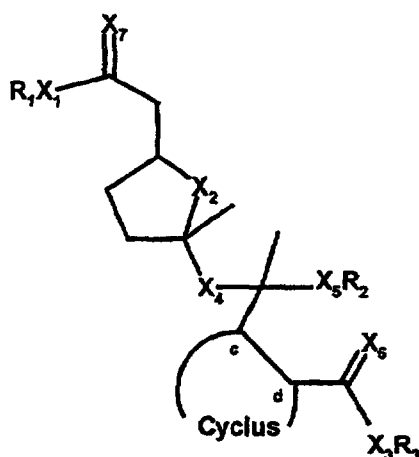


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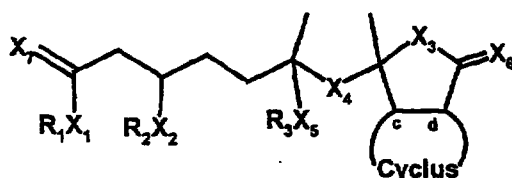
or K and L form, together with the respective carbon atoms to which they are bound, a group of the formula VI, VII or VIII below:

10





VII



VIII

5

wherein

R_1 and R_3 are independently a cation, H, alkyl or aryl,

R_2 is H, alkyl, aryl or acyl,

10 $X_1, X_2, X_3, X_4, X_5, X_6$ and X_7 are independently O, NH, N-alkyl or S, and the cyclus ring is, together with the C-atoms marked ,c' and ,d', an optionally substituted saturated, partly unsaturated or aromatic, carbocyclic or heterocyclic, simple or condensed ring system,

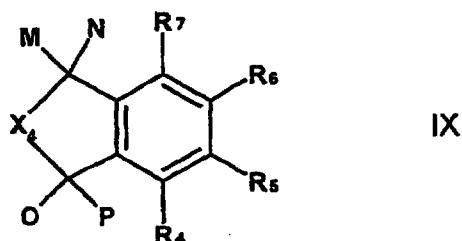
with the exclusion of the compound where K is a group of the formula II and L

is a group of the formula IV in which $X_1, X_2, X_3, X_4, X_5, X_6$ and X_7 are O, R_1, R_2

15 and R_3 are H, R_4 is OH, R_5, R_6 and R_7 are H and cyclus is 3, 8, di-hydroxy anthraquinone, and the compound where K and L form together a group of the formula VI in which $X_1, X_2, X_3, X_4, X_5, X_6$ and X_7 are O, R_1 is CH₃, R_2 and R_3 are H, R_4 is OH, R_5, R_6 and R_7 are H and cyclus is 3, 8, di-hydroxy anthraquinone

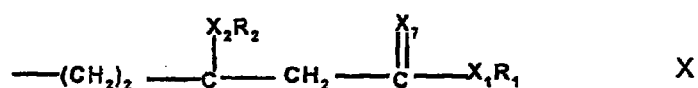
and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

5 The present invention furthermore includes compounds of the general formula IX



wherein

M is a group of the formula X



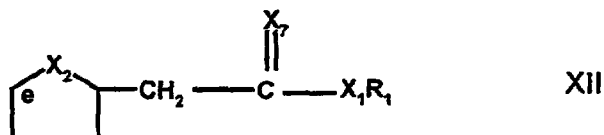
10 and,

N is a group of the formula XI



or M and N form, together with the C atom to which they are bound, a residue of the formula XII

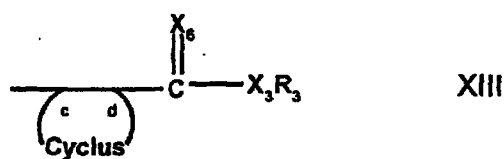
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which is bonded through the C atom marked ,e',

20

O is a group of the formula XIII

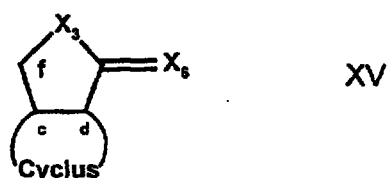


and

P is a group of the formula XIV



or O and P form, together with the C atom to which they are bound, a residue of the formula XV



which is bonded through the C atom marked ,f',
and wherein R₁ to R₇, X₁ to X₇, cyclus, c and d are as defined in claim 1,
and its pharmaceutically acceptable salts, esters and ethers and other
obvious chemical equivalents in all their stereoisomeric and tautomeric forms
and mixtures thereof in any ratio.

The term 'alkyl' as used herein represents a straight or branched, optionally
substituted C₁-C₆-alkyl, preferably a C₁-C₄-alkyl such as: methyl, ethyl, n-
propyl, i-propyl, n-butyl or i-butyl, a straight or branched, optionally
substituted, C₂-C₆-alkenyl, preferably C₂-C₄-alkenyl such as allyl, a straight or
branched, optionally substituted C₂-C₆-alkynyl, preferably C₂-C₄-alkynyl such
as allylene.

The term 'aryl' as used herein represents an optionally substituted benzyl or
phenyl.

The term 'acyl' as used herein represents an optionally substituted aliphatic, aromatic or heterocyclic acyl, for example C₁-C₄aliphatic acyl, such as acetyl or propionyl, aromatic acyl, such as, benzoyl or toluyl, and heterocyclic acyl which is derived from 5- or 6-membered rings with 1-4 hetero atoms, such as, nicotinoyl, furyl, pyrrolyl, thienyl, thiazolyl and oxazolyl.

'Optionally substituted' as used herein means that the group in question is optionally substituted by one or more, preferably 1, 2, 3 or 4, identical or different substituents selected from: hydroxyl, C₁-C₄alkyl, C₁-C₄alkenyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkoxycarbonyl, carbamoyl, carboxyl, trifluoromethyl, cyano, nitro, amino, C₁-C₄alkylamino, diC₁-C₄alkylamino, amidino, aryloxy, arylamino and halogen.

Halogen represents I, Br, Cl or FI, preferably Cl or Br.

The term 'cation' represents an inorganic metal ion or an organic ammonium ion. Examples which may be mentioned are, in particular, pharmacologically acceptable alkali metal ions or alkaline earth metal ions, preferably sodium, potassium, calcium or magnesium ion, the ammonium ion and, from the organic ammonium ions, in particular, an optionally substituted alkylated ammonium ion, such as, for example, the triethylammonium or diethanolammonium ion, as well as the morpholine, benzylammonium and procaine, L-arginine and L-lysine ion.

The cyclus ring, which includes the carbon atoms marked 'c' and 'd' as used in the formulae may represent an optionally substituted, saturated, partly unsaturated or aromatic, carbocyclic or heterocyclic, simple or condensed ring system. A simple ring system means a monocyclic ring containing 3 to 6 ring atoms and a condensed ring system means a condensed dicyclic or tricyclic ring containing 6 to 14 ring atoms.

The saturated carbocyclic ring system may represent a 3 to 14 membered ring system, preferably a simple 3 to 8 membered ring such as cyclo-C₃-C₈alkyl, more preferably cyclo-C₃-C₆alkyl, for example, cyclopropyl, cyclobutyl,

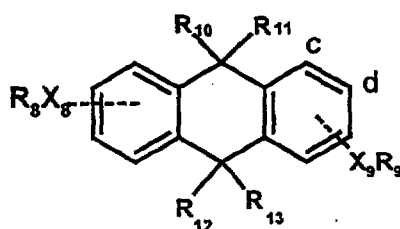
cyclopentyl or cyclohexyl. It may also represent a bi- or tri-cyclic condensed ring system such as bicyclo[3.3.1]nonane and tetradecahydrophenanthrene.

The partly unsaturated carbocyclic ring system differs from the saturated carbocyclic ring system in having one or two double or triple bonds. Thus it may represent a 3 to 14 membered ring system, preferably a 3 to 8 membered ring such as cyclo-C₃-C₈alkene, for example, cyclopentadiene or cyclooctatetraene, more preferably cyclo-C₃-C₆alkene, or cyclo-C₅-C₈alkyne.

The aromatic carbocyclic simple or condensed ring system may represent a 5 to 14 membered monocyclic, dicyclic or tricyclic ring system such as phenyl, naphthyl, phenanthrene or anthraquinone.

The heterocyclic ring system may be saturated, partly unsaturated or aromatic and may be a simple or condensed ring system as defined above. The heterocyclic ring system represents the carbocyclic ring system as defined above in which 1, 2, 3 or 4 of the C atoms are replaced by identical or different heteroatoms selected from N, O and S. It may, for example, represent a 5- or 6-membered ring which has 1 to 4 hetero-atoms, selected from O, S and N, in particular N, optionally together with S or O as ring atoms. Some examples of heterocyclic ring systems are heteroalkyls such as pyrrolidine, piperidine, tetrahydrofuran, oxazolidine and thiazolidine, and heteroaryl residues such as pyridyl, pyrimidyl, furanyl, benzothiazoyl, benzofuranyl and indolyl.

Preferably, the cyclus ring is a group of the formula XVI



XVI

wherein

R_8 is H, alkyl, aryl or acyl,

R_9 is a cation, H, alkyl, aryl or acyl,

R_{10} , R_{11} , R_{12} and R_{13} are independently H, alkyl, $-X_{10}H$ or $-X_{10}R$, or R_{10} and

5 R_{11} and/or R_{12} and R_{13} together are $=X_{10}$,

X_8 , X_9 and X_{10} are independently O, NH or N-alkyl or S,

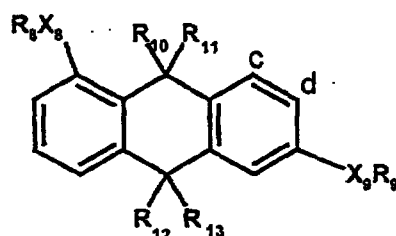
R is alkyl, aryl or acyl,

'-----' is an optional bond, and

the cyclus is bound by the C-atoms marked 'c' and 'd'.

10

More preferably the cyclus ring is a residue of the formula XVIA



XVIA

wherein

15 X_8 and X_9 are independently H or O,

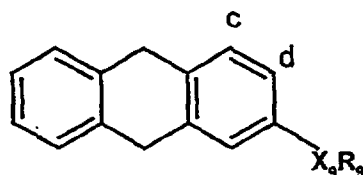
R_8 and R_9 are independently H or alkyl,

R_{10} to R_{13} are H, or R_{10} and R_{13} together and/or R_{12} and R_{13} together are = O,

and the cyclus is bound by the C-atoms marked 'c' and 'd'.

20

The cyclus part of the structure may be any one of a variety of different ring structures. It is advantageous, however, to have a substitution, preferably hydroxyl or alkoxy, on the cyclus. The cyclus is preferably an aromatic ring structure of the formula XVIB below:



XVIB

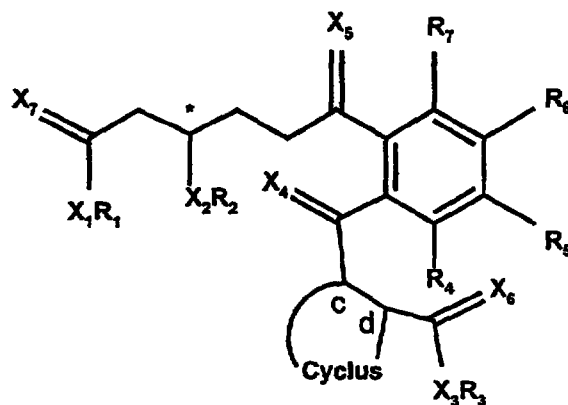
25

wherein

R_9 is H or C_1 - C_4 -alkyl, and

X_9 is O

5 Preferred compounds of the present invention have the general formula XVIII below:



XVIII

wherein

10 R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, with the exclusion of the compound where X_1 to X_7 are O, R_1 , R_2 and R_3 are H, R_4 is OH, R_5 , R_6 and R_7 are H and cyclus is 3, 8, di-hydroxy anthraquinone, and its pharmaceutically acceptable salts, esters and ethers and other obvious equivalents, in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

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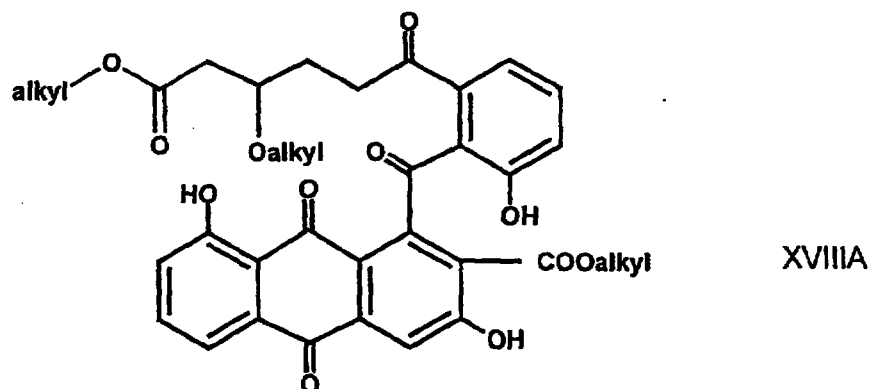
Preferably the carbon marked with an asterisk has an S configuration, in which case the exclusion mentioned above is not applicable.

Suitably, R_1 , R_2 and R_3 are C_1 - C_6 -alkyl, preferably C_1 - C_4 alkyl, such as methyl.

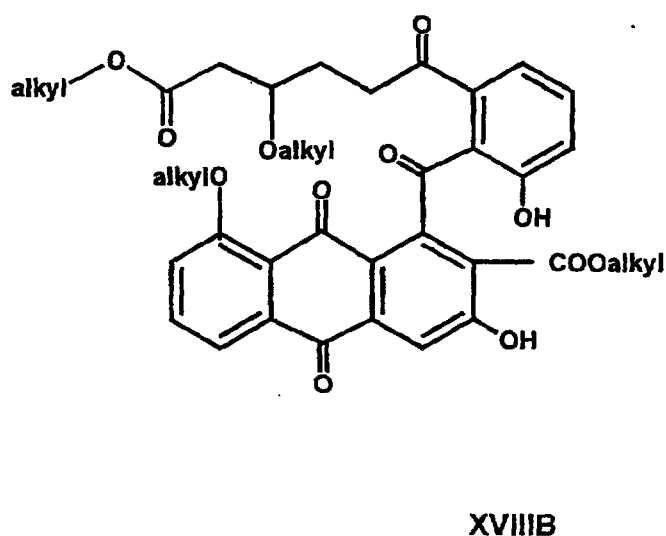
20

Conveniently, any one or more of X_1 to X_7 are O.

An example of a compound of the formula XVIII above is given below:



A further example of a compound of the formula XVIII B above is given below:



The alkylated mumbaisatin derivatives of the formula XVIII A and formula XVIII B are obtained by dissolving mumbaistatin in a solvent, preferably an organic solvent such as alkanol, for example methanol, and reacting with an alkylating agent such as diazoalkane, for example diazomethane, diazoethane, or diarylmethyldiazomethane such as diphenyldiazomethane. The alkyl substituent in the above compounds of the formula XVIII A and formula XVIII B is preferably a C₁-C₄-alkyl. When the C₁-C₄-alkyl is methyl, for example, the methylated mumbaistatin derivatives may be obtained by reacting mumbaistatin in solution with a methylating agent such as diazomethane.

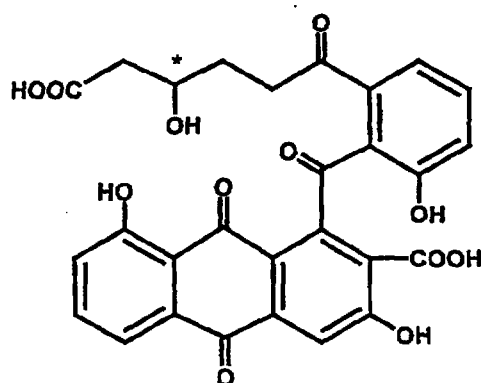
The mumbaistain has ideally previously been treated with acid, preferably low molecular organic acid, for example formic acid, acetic acid or trifluoroacetic acid. The reaction product is subsequently isolated, preferably by chromatography.

5

Isolation of the compounds according to the present invention from the reaction medium can be effected by methods which are in themselves known and which depend on the solubility of the resulting compounds.

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A further example of a compound of the formula XVIII is the diastereomer given below:

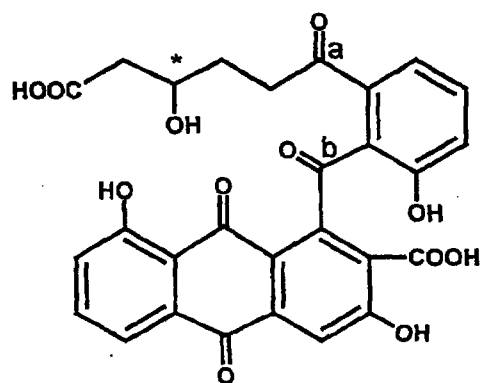


XVIII C

15

wherein the C atom marked with an asterisk has the S configuration.

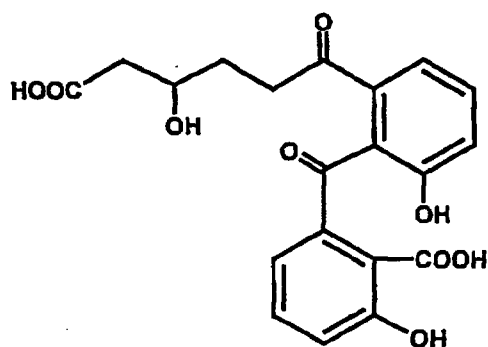
A diastereomer of the formula XVIII D according to the present invention is shown below:



XVIII D

wherein the carbon atoms marked 'a' and 'b' in form of a half-ketal or ketal have independently the S or R configuration.

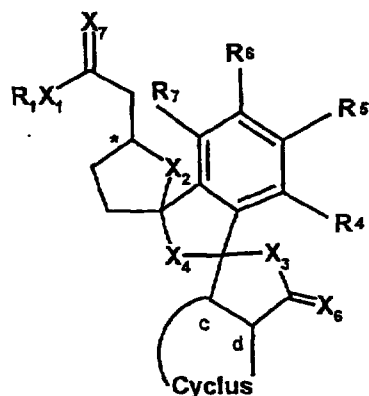
5 A further example of the compound of the formula XVIII is given below:



XVIII

10 Some of the preferred compounds of the formula I exemplified above may be generalised as hydroxy-diketo-dicarboxylic acid derivatives.

The invention further relates to compounds of the general formula XIX below:



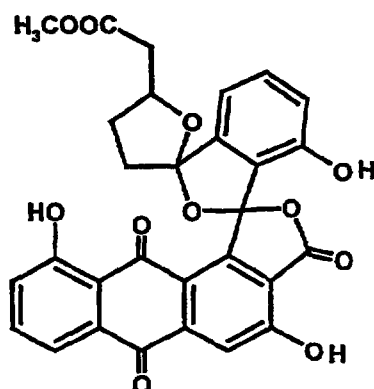
XIX

15 wherein R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, with the exception of the compound where R_1 is methyl, R_4 is $-OH$, $X_1 - X_7$ are O and the cyclus is 3, 8, di-hydroxy anthraquinone, and

its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

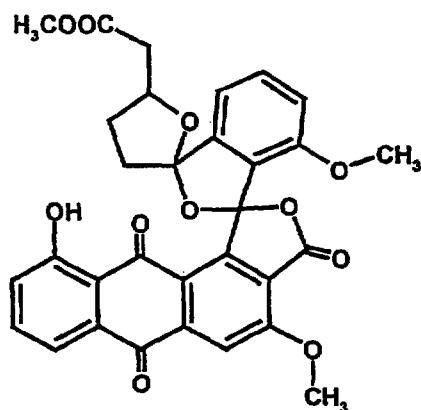
5 Preferably, R₁ is C₁-C₆-alkyl, such as methyl. R₄ is suitably hydroxy or C₁-C₆-alkoxy, such as methoxy.

An example of a compound of the formula XIX is given below:



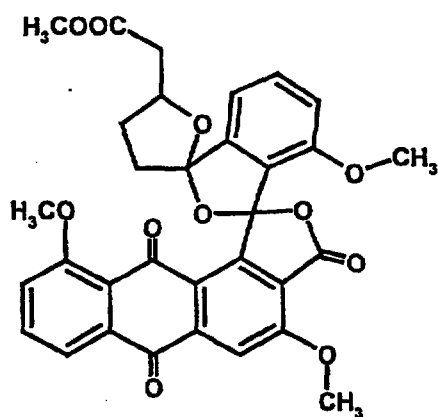
XIXA

A further example of a compound of the formula XIX is given below:



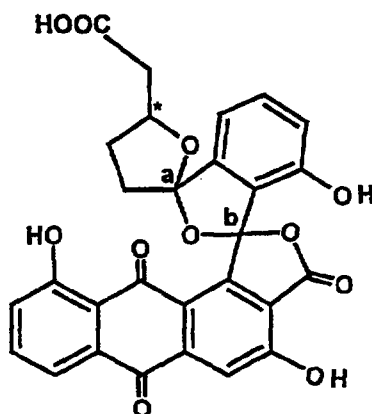
XIXB

A yet further example of a compound of the formula XIX is given below:



XIXC

5 Another example of a compound of the formula XIX is the diastereomer below:



XIXD

10 wherein the C atom marked with an asterisk * has an 'S' configuration and the C atoms marked respectively with 'a' and 'b' both have either an S or R configuration.

15 One process for the preparation of a compound of the formula XIXA, XIXB or XIXIC comprises dissolving mumbaistatin in a solvent, preferably an organic solvent, for example an alkanol such as methanol, and reacting with a

methylating agent such as diazomethane. Mumbaistatin has ideally previously been treated with acid such as trifluoroacetic acid. The reaction product is isolated, preferably by chromatography.

Mumbaistatin is of limited stability in solution at a pH of around 6 to 9. At acid pH mumbaistatin rapidly undergoes a complex conversion, for example to the compound of the formula XIXD above. Because the acid form of mumbaistatin is reacted with diazomethane to produce the methylated compounds of the formula XVIIIA, XVIIIIB, XIXA, XIXB and XIXC above, special precautions need to be taken to ensure that native, defined methylation products are obtained. It has been found that the required methylation products are obtained under cold conditions such as at temperatures of -1°C to 3°C , preferably 0°C , and/or when the process is carried out without prolonged reaction times. It has surprisingly been possible to crystallize at least one of the methylation products by using a mixture of water and acetonitrile. This enabled determination of the structure of the compounds by X-radiation spectrometry.

Table 1:

Crystal data and structure refinement for trimethyl-mumbaistatin (formula XVIIIA).

Identification code	sh608	
Empirical formula	$\text{C}_{33} \text{H}_{27} \text{N} \text{O}_{11}$	
Formula weight	613.56	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	$a = 12.907(4) \text{ Å}$	$\alpha = 90^{\circ}$.
	$b = 11.253(5) \text{ Å}$	$\beta = 96.56(2)^{\circ}$.
	$c = 20.003(6) \text{ Å}$	$\gamma = 90^{\circ}$.
Volume	$2886.2(17) \text{ Å}^3$	

Z	4
Density (calculated)	1.412 Mg/m ³
Absorption coefficient	0.107 mm ⁻¹
F(000)	1280
Crystal size	0.04 x 0.1 x 0.2 mm ³
Theta range for data collection	2.08 to 20.83°.
Index ranges	-12<= <i>h</i> <=12, -11<= <i>k</i> <=11, -19<= <i>l</i> <=19
Reflections collected	9796
Independent reflections	5833 [R(int) = 0.0447]
Completeness to theta = 20.83°	98.7 %
Absorption correction	maximum: 0.862, minimum: 0.632
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5833 / 1 / 822
Goodness-of-fit on F ²	1.064
Final R indices [<i>I</i> >2σ(<i>I</i>)]	R1 = 0.0510, wR2 = 0.0966
R indices (all data)	R1 = 0.0981, wR2 = 0.1171
Absolute structure parameter	1(2)
Extinction coefficient	0.0035(4)
Largest diff. peak and hole	0.194 and -0.174 e.Å ⁻³

Table 2.

Chemical shift of tetramethyl-mumbaistatin lactone di-spiroketone (Formula XIXC in CDCl₃ at 280 K).

	A ^{a)}	B ^{a)}	A	B
	¹ H	¹ H	¹³ C	¹³ C
1	-	-	159.50	159.51
1-OMe	3.87	3.87	56.28	56.28
2	7.26	7.26	118.27	118.27
3	7.67	7.67	134.57	134.57
4	7.85	7.85	119.32	119.32
5	-	-	134.44	134.44
6	-	-	183.27	183.24
7	-	-	139.57	139.57
8	-	-	124.51	124.50
9	-	-	180.29	180.26
10	-	-	122.56	122.50
11	7.88	7.88	110.55	110.58

12	-	-	160.33	160.33
12-OMe	4.21	4.20	57.00	57.00
13	-	-	121.33	121.28
14	-	-	149.95	149.81
15	-	-	164.43	164.15
16	-	-	111.33	111.33
17	-	-	126.62	126.34
18	-	-	153.44	153.39
18-OMe	3.54	3.54	55.52	55.52
19	6.76	6.77	110.97	110.92
20	7.46	7.47	132.15	132.23
21	7.12	7.09	114.38	114.32
22	-	-	141.76	142.18
23	-	-	119.28	119.58
24	2.74/2.58	2.70/2.63	36.05	35.22
25	2.41/1.92	2.41/1.97	30.36	29.87
26	4.77	4.77	77.64	76.54
27	2.90/2.63	2.86/2.63	41.46	40.15
28	-	-	171.74	171.21
28-OMe	3.67	3.71	51.72	51.78

a) A and B correspond to both diastereomer forms (ratio A:B approx. 1.2 :1.0).

Table 3

Comparison of the aromatic protons of formula XVIII A and formula XVIII B.

Position	Formula XVIII A	Formula XVIII B
2	7.29	7.26
3	7.59	7.67
4	7.85/7.84	7.85
11	7.91/7.90	7.88
19	6.92	6.76/6.77
20	7.68/7.67	7.46/7.47
21	6.92	7.12/7.09

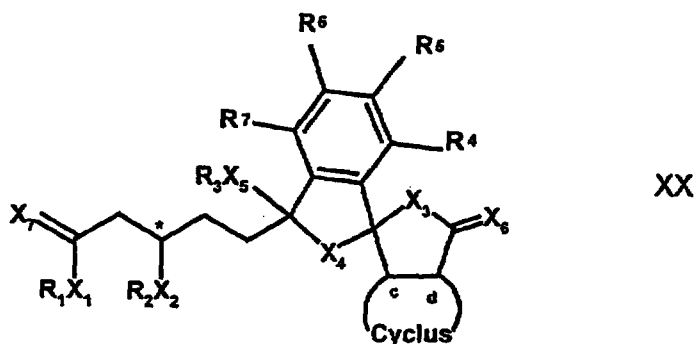
Table 4

Chemical shift of Mumbaistatin lactone-di-spiroketal-monomethylester (formula XIX A) in DMSO at 300K.

Position	XIX A ¹ H	XIX A ¹³ C
1	-	161.38
1-OH	13.26	-
2	7.18	123.82
3	7.62	135.15
4	7.57	117.95
5	-	132.68

6	-	183.53
7	-	138.70
8	-	117.91
9	-	183.09(broad)
10	-	116.48
11	7.16(broad)	~122.1(broad)
12	-	153.87(broad)
12-OH	broad	-
13	-	a)
14	-	a)
15	-	166.45(broad)
16	-	110.11
17	-	124.64, 124.51
18	-	151.14, 151.09
18-OH	9.51, 9.52	-
19	6.68	115.32
20	7.26, 7.27	130.72, 130.78
21	6.97, 6.95	112.45
22	-	143.49, 143.68
23	-	117.93, 118.01
24	2.53/2.45, 2.59/2.37	~35.8(broad), ~34.9(broad)
25	2.26/1.74, 2.22/1.85	~29.8(broad) ~29.4(broad)
26	4.60, 4.54	76.84, 75.91
27	2.68, 2.63	41.09, 39.88
28	-	170.97, 170.86
28-OMe	3.59, 3.61	51.22, 51.28

- a) For these nuclei no signal was observed in the ^{13}C -Spectrum.
- 5 Where two sets of signals were observed (ratio approx. 1.1:1.0) they corresponded to the two diastereomer forms. Both values are separated by a comma in the case where the diastereomers show different chemical shifts (the first value corresponds to the main component).
- 10 The invention also relates to a compound of the general formula XX

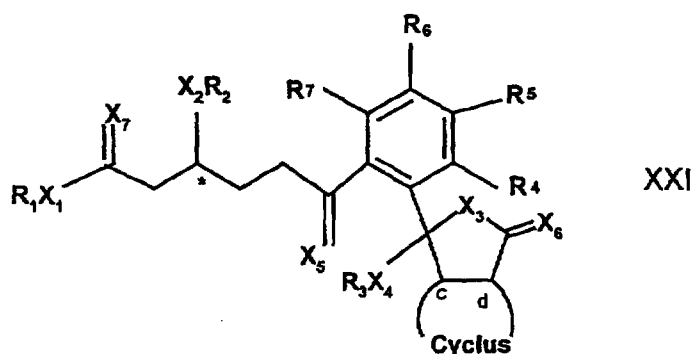


wherein R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, and its
 pharmaceutically acceptable salts, esters and ethers and other chemical equivalents,
 5 in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

Preferably one or more of X_1 to X_7 are O.

The invention furthermore relates to compounds of the general formula XXI :

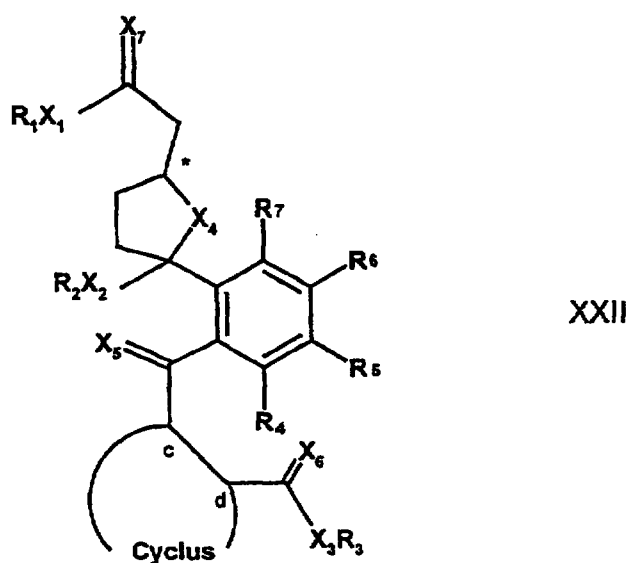
10



wherein
 R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, and
 15 its pharmaceutically acceptable salts, esters and ethers and other obvious chemical
 equivalents, in all their stereoisomeric and tautomeric forms and mixtures thereof in
 any ratio.

Preferably one or more of X_1 to X_7 are O.

The invention additionally relates to a compound of the general formula XXII



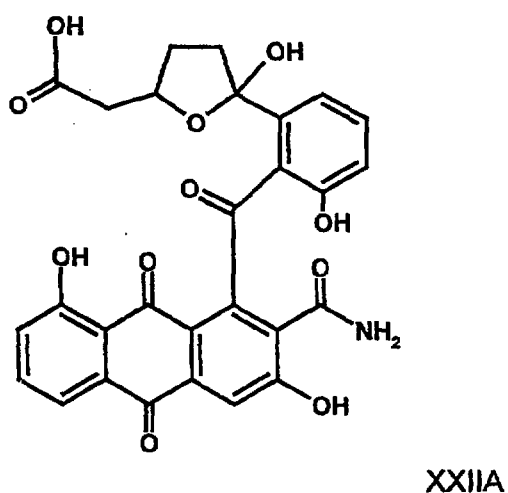
wherein

- 5 R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents, in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

Preferably one or more of X_1 to X_7 are O.

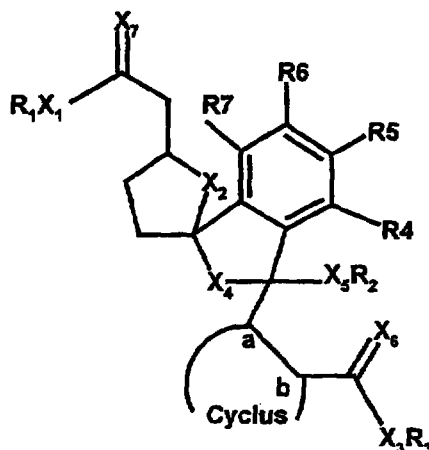
10

An example of a compound of the formula XXII is given below:



A process for the preparation of a compound of the formula XXIIA comprises dissolving mumbaistatin in a solvent, preferably an organic solvent such as alkanol, and reacting with an amide source such as an ammonia solution. The process is carried out under cold conditions, preferably at a temperature of -1°C to 3°C , more preferably at 0°C . The reaction product is subsequently isolated.

The invention furthermore relates to compounds of the general formula XXIV



XXIV

10 wherein

R_1 to R_7 , X_1 to X_7 , cyclus and c and d are as defined above, and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents, in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

15

Preferably, one or more of X_1 to X_7 are O.

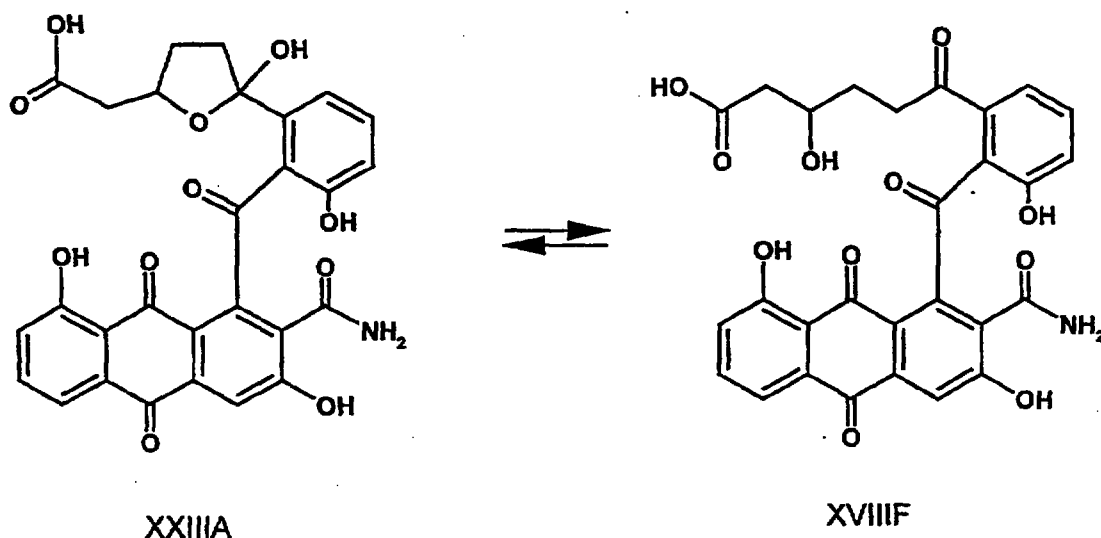
The compounds according to the present invention are tautomers in which open and closed forms exist in equilibrium.

20

The closed structures of the formula XIX to XXIV above can be converted to the open structure of the formula XVIII by reaction with a suitable base. Suitable bases which can be used for the reaction are inorganic or organic bases. Thus, tertiary amines and alkali metal carbonates, such as sodium carbonate, sodium

bicarbonate, potassium bicarbonate, potassium carbonate, lithium carbonate may be used.

An Example of tautomers according to the present invention in equilibrium are
 5 compounds of the formula XXIIIA and XVIIIIF shown below:



The compounds according to the invention may be converted into pharmaceutically acceptable salts and obvious chemical equivalents, like esters and ethers, which are
 10 all covered by the present invention. The invention also covers all salts and obvious chemical equivalents of the present compounds which themselves are not suitable for use as pharmaceuticals but which can be used as intermediates in the preparation of pharmaceutically acceptable salts and derivatives. The invention covers the present aromatic di-keto derivatives and their salts, esters, ethers and
 15 other obvious chemical equivalents in all their stereoisomeric forms and tautomeric forms. The salts of the derivatives (e.g. Na, K, ammonium salts) can be prepared by standard procedures known to one skilled in the art. Salts like sodium and potassium salts, for example, may be prepared by treating the present compounds with suitable sodium or potassium bases.

20

Esters may be prepared, for example, by reacting the present compounds with carboxylic acids in the presence of reagents such as dicyclohexylcarbodiimide

(DCC), or by treating the compound with acylating agents such as acid chlorides. Other methods of preparation of esters are given in the literature, for example in J. March, Advanced Organic Synthesis, 4th Edition, John Wiley & Sons, 1992.

- 5 Ethers may be prepared, for example, from Mumbaistatin by reaction with alkylating agents under basic conditions. Other methods of preparation of ethers are given in the literature, for example in Advanced Organic Synthesis, 4th Edition, J. March, John Wiley & Sons, 1992.
- 10 Other obvious chemical equivalents include reduction or oxidation products and addition products such as hydrates. For example, the anthraquinone group of mumbaistatin may be reduced with a reducing agent to hydroquinone. The resultant product is an effective inhibitor of glucose-6-phosphate translocase with an IC_{50} of ~ 5 nM.

15

Glucose-6-phosphate translocase activity has been shown in several biochemical test systems for mumbaistatin. The yield of mumbaistatin from the culture filtrate of *Streptomyces litmocidini* is extremely low, however, which has hindered further development of the compound. Moreover, until now it has not been possible to

20 ascertain the structural formula of mumbaistatin due of numerous factors including the compounds inability to crystalize and instability in solution.

A process has now been found, however, which enables the isolation of mumbaistatin from an extract in relatively high yield. The present invention

25 accordingly provides a process for the isolation of mumbaistatin comprising extracting a culture filtrate including mumbaistatin by ion exchange chromatography at a pH of 5-8, preferably 6 or 7. Although the use of ion exchange is generally mentioned in PCT/EP99/04127, it is clear that the use of ion exchange for the purpose of improving yield was not recognised. This is seen from the examples in

30 the above patent application PCT/EP99/04127 where ion exchangers are not used for the isolation of mumbaistatin and where from 730 litres of culture filtrate merely 70 mg of pure mumbaistatin is obtained. The process of the present invention allows the isolation and enrichment of mumbaistatin and mumbaistatin-related compounds by means of an ion exchange process whereby yields of at least more than 50 %,

more usually > 70 % are obtained. Mumbaistatin obtained according to the present process has an improved IC_{50} of ≈ 5 nM in comparison to the mumbaistatin obtained in PCT/EP99/04127.

- 5 In the process for the isolation of mumbaistatin according to the present invention various ion exchangers may be used. Examples are QAE-, DEAE- and THAE-anion exchangers. Preferably, substituted or unsubstituted amino groups are carried on the chosen matrix. More preferably, DEAE-anion exchangers are used such as DEAE-
10 ®Sephacrose Fast Flow or ®Fractogel EMD DEAE. The anion exchangers may be used in a known manner. An organic solvent content of 5 to 85 % in a buffer system may be used. It is preferable, however, that the organic solvent used has a high content of buffer system, preferably therefore, an organic solvent content of 10 to 40 % in the aqueous buffer solution is used. Examples of suitable organic solvents are
15 water-miscible organic solvents such as lower alcohols, acetone, acetonitrile, glycol, dioxane, dimethyl sulfoxide, formamide and the like. Preferred solvents are methanol, ethanol, isopropanol and acetone.

- With the process described, > 99% pure mumbaistatin can be obtained and the compound can be enriched in a yield of more than 70 %. The resultant enriched
20 mumbaistatin may be purified in a simple manner by, for example, molecular sieve- and/or reverse-phase-chromatography.

- The compounds according to the invention inhibit rat liver microsomal glucose-6-phosphate translocase. The compounds are therefore useful as pharmaceutically
25 active ingredients, in particular in the treatment of diabetes mellitus, and more generally in the treatment or prophylaxis of conditions which are caused by or associated with an elevated activity of glucose-6-phosphate translocase, or of conditions in which it is intended to reduce glucose-6-phosphate translocase activity. The compounds according to the present invention and their pharmaceutically
30 acceptable salts, esters, ethers and other obvious chemical equivalents can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals on their own, in mixtures with one another and in the form of pharmaceutical compositions which permit enteral or parenteral administration.

Accordingly, the present invention also relates to aromatic di-keto derivatives and their pharmaceutically acceptable salts, esters, ethers and others obvious chemical equivalents for use as pharmaceuticals and to the use of the derivatives and their pharmaceutically acceptable salts, esters, ethers and other obvious chemical equivalents for the production of medicaments for reducing glucose-6-phosphate translocase activity, in particular for the production of medicaments for the treatment of diabetes mellitus. The present invention further relates to pharmaceutical compositions which contain an effective amount of the derivatives and/or one or more pharmaceutically acceptable salts, esters, ethers and/or obvious chemical equivalents thereof together with a pharmaceutically acceptable carrier.

The compounds according to the invention can be administered orally, intramuscularly, intravenously or by other modes of administration. Pharmaceutical compositions which contain the present compounds or a pharmaceutically acceptable salt or obvious chemical equivalent thereof singly or in combinations can be prepared according to standard techniques by mixing the compound(s) with one or more pharmacologically acceptable excipients and/or auxiliaries such as, for example, fillers, emulsifiers, lubricants, masking flavours, colorants or buffer substances, and converting the mixture into a suitable pharmaceutical form such as, for example, tablets, coated tablets, capsules or a suspension or solution suitable for enteral or parenteral administration.

Examples of auxiliaries and/or excipients which may be mentioned are starch, tragacanth, lactose, talc, agar-agar, polyglycols, ethanol and water. Suitable and preferred for parenteral administration are suspension or solutions in water. It is also possible to administer the active substances as such, without vehicles or diluents, in a suitable form, for example, in capsules. Pharmaceutical compositions comprising one or more of the present compounds or a pharmaceutically acceptable salt or obvious chemical equivalent may also contain other pharmaceutically active ingredients.

As customary, the galenic formulation and the method of administration as well as the dosage range which are suitable in a specific case depend on the species to be treated and on the state of the respective condition or disease, and can be optimized

using methods known in the art. On an average, the daily dose of a compound according to the present invention in a patient of about 75 mg weight is at least 0.001 mg to at most 100 mg, preferably at most 10.0 mg.

- 5 Apart from use as pharmaceutically active ingredients and as intermediates in the production of derivatives, the present compounds and their salts and obvious chemical equivalents can also be employed as auxiliaries for diagnostic purposes, for example in *in vitro* diagnoses, and for research purposes in biochemical investigations in which an inhibition of glucose-6-phosphate translocase is desired.

10

The following examples are illustrative of the present invention, but not limitative of the scope thereof.

Abbreviations: MeOH methanol; DMSO dimethylsulfoxide; TFA trifluoroacetic acid

15

Example 1

Maintenance of the culture *Streptomyces litmucidini*, DSM 11641.

- 20 Culture DSM 11641 was maintained on the following medium :

	Malt extract	:	10.0 g
	Yeast extract	:	4.0 g
	Glucose	:	4.0 g
25	Agar powder	:	13.0 g
	Demineralized water	:	1.0 litre
	pH	:	7.0

- 30 After dissolving the above mentioned ingredients thoroughly by heating, it was distributed in test tubes and then sterilized at 121°C for 20 minutes. The test tubes were then cooled and allowed to solidify in a slanting position. The agar slants were streaked with the growth of the culture *Streptomyces litmucidini*, DSM 11641, by a

wire loop and incubated at 28°C ($\pm$ 1°C) until a good growth was observed. The well grown cultures were stored in the refrigerator at 8°C.

Example 2

5

Fermentation of culture *Streptomyces litmocidini*, DSM 11641 in fermenters.

Stage 1: Preparation of seed culture in shake flasks

10 Composition of seed medium :

	Glucose	:	15.0 g
	Soyabean meal	:	15.0 g
	Corn steep liquor	:	5.0 g
	NaCl	:	5.0 g
15	CaCO ₃	:	2.0 g
	Demineralized water	:	1.0 litre
	pH	:	7.0

The above seed medium was distributed in 160 ml amounts in 1 L Erlenmeyer flasks
20 and autoclaved at 121°C for 20 minutes. The flasks were cooled to room temperature and each flask was then inoculated with a loopful of the above mentioned well grown culture of Example 1 and shaken on a rotary shaker for 72 hours at 240 rpm at 27°C ($\pm$ 1°C) to give seed culture.

25 Composition of the production medium

	Glucose	:	20.0 g
	Soyabean meal	:	10.0 g
	CaCO ₃	:	0.2 g
	Cobalt chloride	:	0.001 g
30	Demineralized water	:	1.0 litre
	pH	:	7.0

Stage 2 : Preparation of seed culture in fermenter

80 litres of the seed medium, as described above, in a 100 litre Marubishi fermenter was sterilised *in situ* for 45 minutes at 121°C, cooled to 27°C ± 1°C and seeded with 4.5 litres of the seed culture mentioned above.

5 The fermentation was run with the following parameters :

Temperature	:	27°C (± 0.5°C)
Agitation	:	80 rpm
Aeration	:	50 lpm
Harvest time	:	24 hours

10

Stage 3 : Large scale fermentation

700 litres of the production medium, as described above, in a 1000 litre Marubishi fermenter along with 150 ml of [®]Desmophen (polypropylene oxide) as antifoam agent was sterilised *in situ* for 45 minutes at 121°C, cooled to 27°C ± 1°C and seeded with 75 litres of the seed culture from Stage 2.

The fermentation was run with the following parameters :

Temperature	:	27°C (± 0.5°C)
20 Agitation	:	50 rpm
Aeration	:	450 lpm
Harvest time	:	40-44 hours

The production of the compound was monitored by measuring the inhibition of glucose-6-phosphate translocase. When fermentation was discontinued, the pH of the culture broth was 6.0 - 7.0. The culture broth was centrifuged after harvesting and the glucose-6-phosphate translocase inhibitor Mumbaistatin was isolated from the culture filtrate as described below in Example 3.

30 Example 3

Isolation of Mumbaistatin by anion exchange

Approximately 200 litres of culture broth was harvested and separated from mycelium (12 kg) by centrifugation. The desired compound Mumbaistatin was found to be present primarily in the culture filtrate. The culture filtrate (180 litres with 120 mg mumbaistatin) was passed over a column filled with adsorption resin [®]MCI GEL CHP20P (20 cm diameter x 45 cm height, content 14 litres). The column was eluted with a gradient process of from 120 litres 0.1% phosphate buffer, pH 6.3 to 120 litres 45% isopropanol in water. The column through-flow was 18 litres/hour. The largest amount of mumbaistatin (102 mg in 12 litres) was present in the salt-free fraction which was eluted with a step gradient of 25 to 28 % isopropanol in water. The resultant active eluate was passed through DEAE-[®]Sepharose Fast Flow filled column (3 litres) which had been equilibrated to pH 7.0 with phosphate buffer. Mumbaistatin was eluted in a gradient process with 20 % isopropanol in 0.1 % sodium phosphate buffer, pH 7.0 as A-buffer and 20 % isopropanol in 0.1 % phosphate buffer and 0.25 % NaCl as B-buffer. Using a flow rate of 50 ml /min., 100 fractions were collected in which fractions 72 to 74 contained 81 mg of highly enriched mumbaistatin and fraction 75 a further 18 mg which was less pure. The fractions were pooled and concentrated in vacuum. The material was further purified by passing through a [®]Nucleosil 100-10 C₁₈AB column (2.1 cm x 25 cm) and eluted at pH 6.3 with a step gradient of 5 – 35 % acetonitrile in 0.05 % ammonium acetate buffer. Freeze drying of the pure fractions resulted in a total of 86 mg (73 + 13 mg) pure mumbaistatin ammonium salt.

The sodium salt of mumbaistatin was prepared by dissolving 40 mg of the ammonium salt in 10 ml water (pH 6.4) and increasing the flow of the solution with sodium chloride to 12 mS/cm². The resultant aqueous solution was then passed over a [®]MCI GEL CHP20P column (1cm wide x 9cm high). The elution results with a water/40% acetonitrile in water gradient, the column flow was 5 ml per minute and the fraction sizes were 10 ml. In fractions 16 to 19 the sodium salt was found and the purified solution had a pH of 8.5. From these fractions resulted 32 mg mumbaistatin sodium salt after freeze-drying with a purity of 99%, measured by HPLC.

UV maxima, dissolved in methanol:

219 nm, ϵ = 33 000;

257 nm, ϵ = 19 500;

285 nm, ϵ = 19 000;

414 nm, ϵ = 5 100.

Inhibition of glucose-6-phosphate translocase from rat liver microsomes was with an
5 IC_{50} of = 5 nM. Inhibition of microsomal glucose-6-phosphatase in 10 μ M solution:
activity was not demonstrable.

Example 4

Mumbaistatin methylation products

10

18 mg mumbaistatin obtained according to Example 3 was dissolved in 50 ml water,
cooled to 0°C and maintained at a pH of 2.8 with cold trifluoroacetic acid (TFA).
Directly thereafter the resultant mixture was passed over a column (1 cm x 8 cm)
filled with 6.2 ml [®]MCI GEL, CHP20P, (75 – 150 μ m), and eluted using a gradient of
15 0.01% TFA to 30 % acetonitrile in 0.01 % TFA. The flow rate was 2.5 ml /min. The
eluates were cooled and the mumbaistatin-containing fractions directly frozen to –
40° C and lyophilised.

The freeze-dried product (15 mg) was dissolved in methanol and methylated with
20 diazomethane. After concentration in vacuum the reaction mixture, a mixture of more
than ten methylation products was separated by passing over [®]LiChrosorb RP18,
10 μ , column with dimensions 1 cm x 25 cm (width x length). Acetonitrile in water, 5
to 55 %, was used as the solution. The fractions were pooled cold and maintained
under cold conditions during further processing. The fractions were concentrated in
25 vacuum. Fraction 19 was mumbaistatin-mono-methylether-dimethyl ester
corresponding to formula XVIII A having a molecular weight of 590. The characteristic
NMR data for the compound are shown in Table 3 above. Inhibition of glucose-6-
translocase by a 3 μ M solution: 42 %.

30 A compound corresponding to formula XIXB was obtained from fraction 34 after
concentration in vacuum under cold conditions. Crystallographic data for the
compound are provided in Table 1 above. There exist the diastereomers S,R,R and

S,S,S for the compound which are shown above. Inhibition of glucose-6-phosphate translocase: $IC_{50} = > 100 \mu M$.

Fraction 26 contained a compound which, after storage, was the mumbaistatin tetramethyl derivative corresponding to formula XIXC. The relevant 1H and ^{13}C -NMR data for this compound are provided in Table 2 above.

Example 5

Mumbaistatin hemiketal-amide (Formula XXIIIA)

10

A 1 ml concentrated aqueous ammonia solution was added dropwise under an argon atmosphere at $0^\circ C$ with stirring to a solution of 10 ml mumbaistatin in 1 ml methanol. The mixture was stirred at this temperature for 2 hours and subsequently the solution was removed in vacuum. 10 mg mumbaistatin-amide was obtained in the form of a beige powder. The molecular weight (548, $M + H^+$) was determined by electron spray mass spectrometry corresponding to the chemical formula $C_{28}H_{21}NO_{11}$.

15

1H -NMR (500 MHz, DMSO- d_6): $\delta = 7.8$ (d, 1H), 7.75 (t, 1H), 7.35 (m, 1H), 7.25 (s, 1H), 6.85 (t, 1H), 6.55 (d, 1H), 3.85 (m, 1H), 2.2-2.35 (m), 2.05 (m, 1H), 1.8 (m, 1H), 1.2-1.4 (m) ppm.

20

Mumbaistatin amide of the formula XXIIIA inhibits glucose-6-phosphate translocase with an $IC_{50} = \sim 1 \mu M$

Example 6

25

Manufacture of mumbaistatin lactone diketal mono-methyl-esters

30

10 mg mumbaistatin obtained from Example 3 was dissolved in 1 ml absolute methanol, reacted with 0.1 % strength aqueous TFA and allowed to stand at room temperature for 5 hours. The reaction product was purified by preparative chromatography as described in Example 3 and after freeze-drying the active fractions contained 7 mg of mumbaistatin lactone mono methyl ester (formula XIXA). The molecular weight of the compound was 544 Da (ESI-MS).

INTERNATIONAL FORM

Hoechst Marion Roussel GmbH
65926 Frankfurt

VIABILITY STATEMENT

issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Hoechst Marion Roussel GmbH Address: 65926 Frankfurt	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11641 Date of the deposit or the transfer: 1997-07-04
III. VIABILITY STATEMENT	
The viability of the microorganism identified under II above was tested on 1997-07-04 ² . On that date, the said microorganism was (X) ³ viable () ³ no longer viable	
IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED⁴	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1997-07-07

¹ Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

² In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.

³ Mark with a cross the applicable box.

⁴ Fill in if the information has been requested and if the results of the test were negative.

INTERNATIONAL FORM

Hoechst Marion Roussel GmbH
65926 Frankfurt

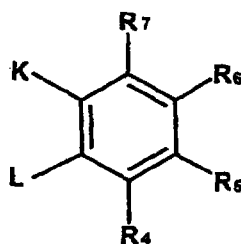
RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: HIL 008003	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM 11641
II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION	
The microorganism identified under I. above was accompanied by: ☐ a scientific description ☒ a proposed taxonomic designation (Mark with a cross where applicable).	
III. RECEIPT AND ACCEPTANCE	
This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1997-07-04 (Date of the original deposit) ¹ .	
IV. RECEIPT OF REQUEST FOR CONVERSION	
The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):  Date: 1997-07-07

¹ Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

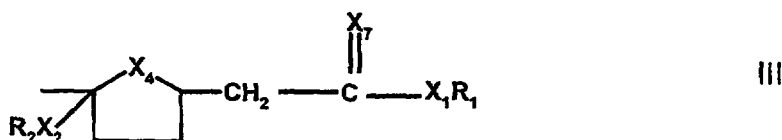
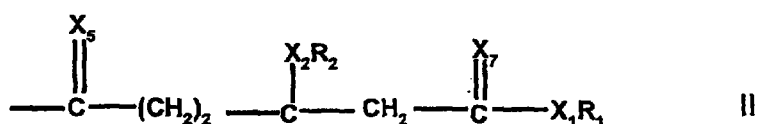
Claims

1. A compound of the formula I



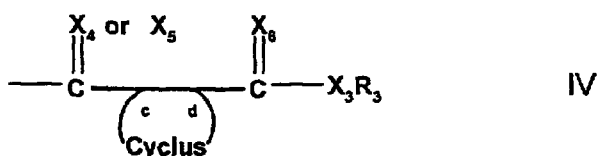
- 5 wherein

R_4 , R_5 , R_6 and R_7 are independently H, OH, halogen, optionally substituted alkyl, aryl or acyl, X-alkyl or X-aryl, where X is O, NH, N-alkyl or S, K is a group of the formula II or III below:

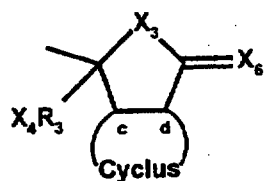


10

L is a group of the formula IV or V below:



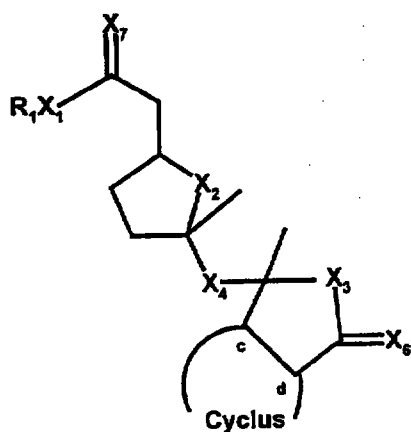
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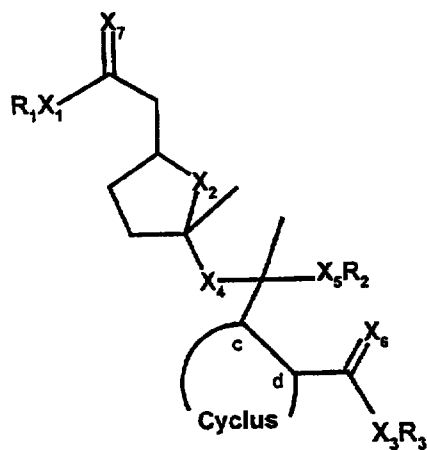
V



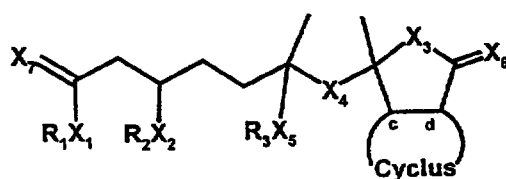
or K and L form, together with the respective carbon atoms to which they are bound, a group of the formula VI, VII or VIII below:



VI



VII



VIII



wherein

R₁ and R₃ are independently a cation, H, alkyl or aryl,

R₂ is H, alkyl, aryl or acyl,

X₁, X₂, X₃, X₄, X₅, X₆ and X₇ are independently O, NH, N-alkyl or S, and the

5 cyclus ring is, together with the C-atoms marked ,c' and ,d', an optionally substituted saturated, partly unsaturated or aromatic, carbocyclic or heterocyclic, simple or condensed ring system,

with the exclusion of the compound where K is a group of the formula II and L

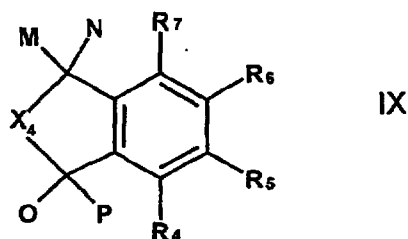
is a group of the formula IV in which X₁, X₂, X₃, X₄, X₅, X₆ and X₇ are O, R₁, R₂

10 and R₃ are H, R₄ is OH, R₅, R₆ and R₇ are H and cyclus is 3, 8, di-hydroxy anthraquinone, and the compound where K and L form together a group of the formula VI in which X₁, X₂, X₃, X₄, X₅, X₆ and X₇ are O, R₁ is -CH₃, R₂ and R₃ are H, R₄ is OH, R₅, R₆ and R₇ are H and cyclus is 3, 8, di-hydroxy anthraquinone,

15 and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

2. A compound as defined in claim 1 of the formula IX

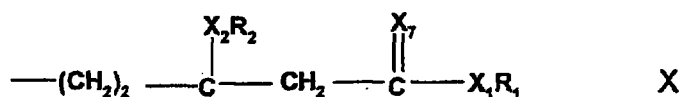
20



wherein

M is a group of the formula X

25

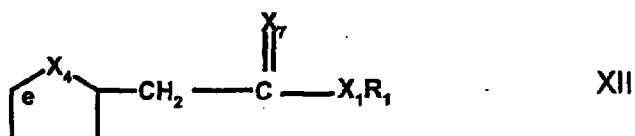


and,

N is a group of the formula XI



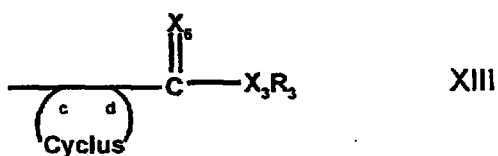
or M and N form, together with the C atom to which they are bound, a residue of the formula XII



10

which is bonded through the C atom marked ,e',

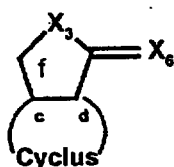
O is a group of the formula XIII



and



or O and P form, together with the C atom to which they are bound, a residue of the formula XV:



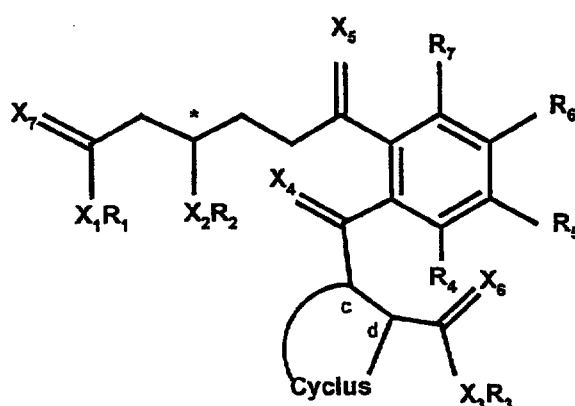
XV



which is bonded through the C. atom marked ,f',
 and wherein R₁ to R₇, X₁ to X₇, cyclus, c and d are as defined in claim 1,
 5 and its pharmaceutically acceptable salts, esters and ethers and other
 obvious chemical equivalents in all their stereoisomeric and tautomeric forms
 and mixtures thereof in any ratio.

3. A compound as defined in claim 1 of the formula XVIII below

10



XVIII

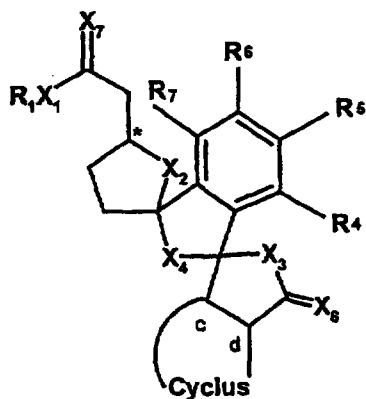
wherein R₁ to R₇, X₁ to X₇, cyclus, c and d, are as defined in claim 1 and its
 pharmaceutically acceptable salts, esters and ethers and other obvious
 chemical equivalents in all their stereoisomeric and tautomeric forms and
 15 mixtures thereof in any ratio.

4. A compound of the formula I as defined in claim 1 or of the formula XVIII as
 defined in claim 3 wherein R₁, R₂ and R₃ are alkyl.



5. A process for the preparation of a compound of the formula XVIII as defined in claim 4, comprising reacting a compound of the formula XVIII wherein R_1 , R_2 and/or R_3 are H with an alkylating agent, and isolating the reaction product.

- 5 6. A compound as defined in claim 1 or claim 2 of the formula XIX below

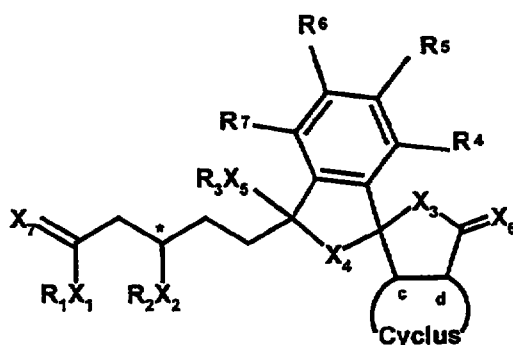


XIX

wherein

R_1 , R_4 to R_7 , X_1 to X_7 , cyclus, c and d are as defined in claim 1,
and its pharmaceutically acceptable salts, esters and ethers and other
obvious chemical equivalents in all their stereoisomeric and tautomeric forms
and mixtures thereof in any ratio.

7. A compound of the formula XIX as defined in claim 6, wherein R_1 is alkyl and R_4 is OH or alkoxy.
8. A process for the preparation of a compound as defined in claim 6, comprising reacting a solution of the compound of the formula XIX wherein R_1 is H and R_4 is OH with an alkylating agent and isolating the reaction product.
9. A process for the preparation of a compound as defined in claim 7, comprising reacting a solution of the compound of the formula XIX wherein R_1 is H and R_4 is OH in an alkyl alcohol with an acid and isolating the reaction product.
10. A compound of the formula XX below as defined in claim 1 or claim 2

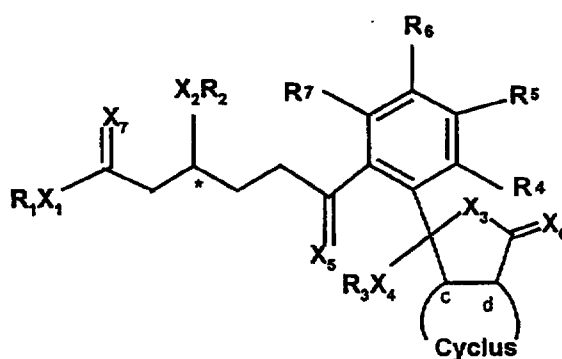


XX

wherein

R_1 to R_7 , X_1 to X_7 , cyclus, c and d are as defined in claim 1 above, and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

11. A compound of the formula XXI below as defined in claim 1

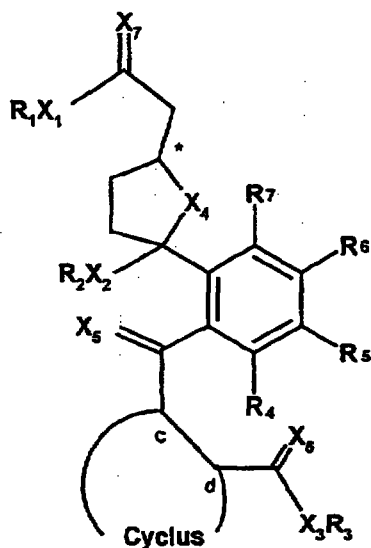


XXI

wherein

R_1 to R_7 , X_1 to X_7 , cyclus, c and d are as defined in claim 1, and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

12. A compound as defined in claim 1 of the formula XXII below



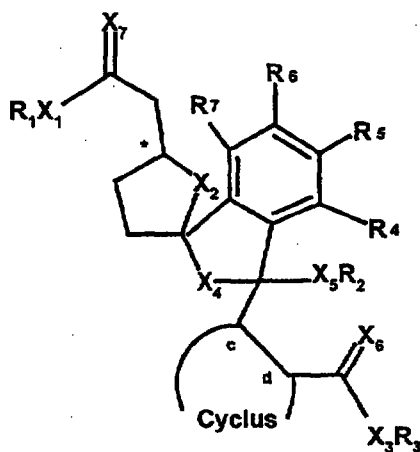
XXII

wherein

X_1 to X_7 , R_1 to R_7 , cycclus, c and d are as defined in claim 1, and its pharmaceutically acceptable salts, esters and ethers and other obvious chemical equivalents in all their stereoisomeric and tautomeric forms and mixtures thereof in any ratio.

13. A compound of the formula XXII as defined in claim 12, wherein R_1 to R_7 are H, X_3 is NH and R_4 is OH.

14. A compound as defined in claim 1 or claim 2 of the formula



XXIV

wherein



R₁ to R₇, X₁ to X₇ and cyclus are as defined in claim 1,
and its pharmaceutically acceptable salts, esters and ethers and other
obvious chemical equivalents in all their stereoisomeric and tautomeric forms
and mixtures thereof in any ratio.

5

15. A process for the preparation of a compound of the formula XVIII, XXII or XXIV as claimed in claims 3, 12 or 14, respectively, wherein -X₃R₃ is -NH₂, comprising reacting a compound of the formula XVIII, XXII or XXIV wherein X₃R₃ is OH with an amide source.

10

16. A process according to claim 15 wherein the compound of the formula XVIII is mumbaistatin.

15

17. A compound as defined in any one of claims 1-4, 6, 7 and 10-14, respectively, wherein any one or more of X₁ to X₇ are O.

18. A compound as defined in any one of claims 3, 4, 6, 7, 10-14, 17, respectively, wherein the carbon marked with an asterisk has an S configuration and the exclusion in claim 1 does not apply.

20

19. A compound as defined in any one of the preceding claims wherein cyclus is a group selected from: optionally substituted phenyl, benzyl, naphthyl, phenanthrene or anthraquinone.

25

20. A compound as defined in claim 19 wherein the cyclus is optionally substituted by one or more of OH, C₁-C₄-alkyl, -OC₁-C₃-alkyl, amino, nitro, halogen, -NH-C₁-C₄-alkyl, carboxy and cyano.

30

21. A compound as defined in claim 19 or 20 wherein the cyclus is 3, 8-dihydroxyanthraquinone.

22. A compound as defined in any one of the preceding claims or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.



23. A pharmaceutical composition, comprising an effective amount of a compound as defined in any one of claims 1 to 4, 6, 7, 10 to 14, 17 to 22 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5

24. A compound as defined in any one of claims 1 to 4, 6, 7, 10 to 14, 17 to 22 or a pharmaceutically acceptable salt thereof for use as an inhibitor of glucose-6-phosphate translocase.

10 25. A compound as defined in any one of claims 1 to 4, 6, 7, 10 to 14, 17 to 22 or a pharmaceutically acceptable salt thereof for use in the treatment of diabetes mellitus.