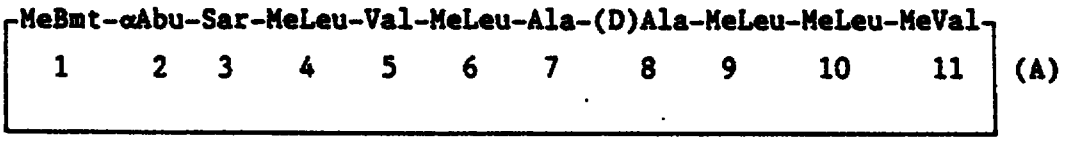
Description

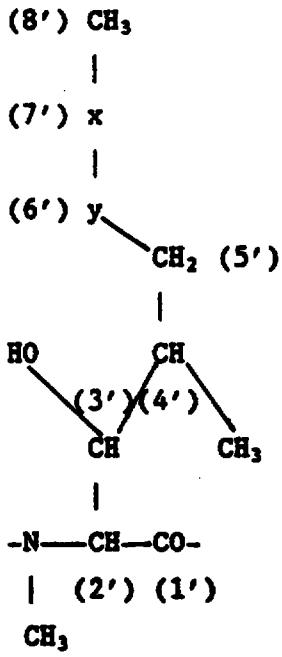
The present invention relates to a new use, in particular a new pharmaceutical use, for cyclosporins, as well as to new cyclosporins as novel compounds per se.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated undecapeptides, generally possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity, each to a greater or lesser degree. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and now commercially available under the Registered Trade Mark SANDIMMUN®. Ciclosporin is the cyclosporin of formula A



(A)

wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which -x-y- is trans -CH=CH- and the positive 2′, 3′ and 4′ have the configuration S, R and R respectively.

Since the original discovery of Ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta, 60, 1247-1255 (1977); Traber et al. 2, Helv. Chim. Acta, 65, 1655-1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240 (1982); and von Wartburg et al. Progress in Allergy, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the dihydro- and iso-cyclosporins [in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y- = -CH_2-CH_2- / the linkage of the residue -MeBmt- to the residue at the 11-position of the cyclosporin molecule (Formula A above) is via the 3′-O-atom rather than the α-N-atom]; derivatised cyclosporins (e.g. in which the 3′-O-atom of the -MeBmt- residue is acylated or a further substituent is introduced at the α-carbon atom of the sarcosyl residue at the 3-position); cyclosporins in which the -MeBmt-residue is present in isomeric form (e.g. in

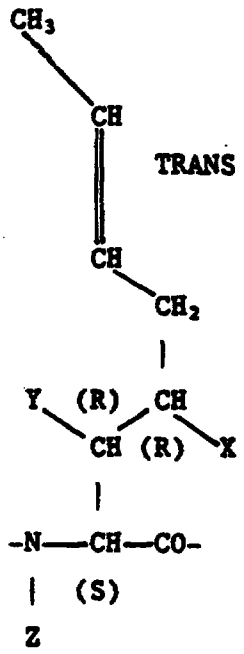
which the configuration across positions 6' and 7' of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger - see e.g. Traber et al. 1, Traber et al. 2 and Kobel et al. loc. cit.; U.S. Patents Nos 4 108 985, 4 210 581, 4 220 641, 4 288 431, 4 554 351 and 4 396 542; European Patent Publications Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transpl. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins is thus now very large indeed and includes, for example [Thr]^{2}-, [Val]^{2}-, [Nva]^{2}- and [Nva]^{2}-[Nva]^{5}-Ciclosporin (also known as cyclosporins C, D, G and M respectively), [3-O-acetyl-MeBmt]^{1}-Ciclosporin (also known as cyclosporin A acetate), [Dihydro-MeBmt]^{1}-[Val]^{2}-Ciclosporin (also known as dihydro-cyclosporin D), [Iso-MeBmt]^{1}-[Nva]^{2}-Ciclosporin (also known as isocyclosporin G), [-(D)Ser]^{8}-Ciclosporin, [MeIle]^{11}-Ciclosporin, [(D)MeVal]^{11}-Ciclosporin (also known as cyclosporin H), [MeAla]-^{6}-Ciclosporin, [(D)Pro]^{3}-Ciclosporin and so on.

[In accordance with conventional nomenclature for cyclosporins, these are defined throughout the present specification and claims by reference to the structure of Ciclosporin (i.e. Cyclosporin A). This is done by first indicating the amino acid residues present which differ from those present in Ciclosporin (e.g. "[(D)-Pro]^{3}" to indicate that the cyclosporin in question has a -(D)Pro- rather than -Sar- residue at the 3-position) and then applying the term "Ciclosporin" to characterise remaining residues which are identical to those present in Ciclosporin.

The residue -MeBmt- at position 1 in Ciclosporin was unknown before the discovery of the cyclosporins. This residue and variants or modifications of it, e.g. as described below, are thus generally characteristic of the cyclosporins. In general, variants or alternatives to [MeBmt]^{1} are defined by reference to the -MeBmt-structure. Thus for dihydrocyclosporins in which the moiety -x-y- (see formula B above) is reduced to -CH_2-CH_2-, the residue at the 1-position is defined as "-dihydro-MeBmt-". Where the configuration across the moiety -x-y- is cis rather than trans, the resulting residue is defined as "-cis-MeBmt-".

Where portions of the -MeBmt- residue are deleted, this is indicated by defining the position of the deletion, employing the qualifier "des" to indicate deletion, and then defining the group or atom omitted, prior to the determinant "-MeBmt-", "-dihydro-MeBmt-", "-cis-MeBmt-" etc.. Thus "-N-desmethyl-MeBmt-", "-3'-desoxy-MeBmt-", and "-3'-desoxy-4'-desmethyl-MeBmt-" are the residues of Formula B^1, B^2 and B^3 respectively:



(B^1, B^2, B^3)

B^1 - X = CH_3, Y = OH, Z = H.
B^2 - X = CH_3, Y = H, Z = CH_3.
B^3 - X = H, Y = H, Z = CH_3.

Where positions or groups, e.g. in -MeBmt-, are substituted this is represented in conventional manner by defining the position and nature of the substitution. Thus -3'-O-acetyl-MeBmt- is the residue of formula B in which the 3'-OH group is acetylated (3'-O-$COCH_3$). Where substituents of groups, in e.g. -MeBmt-, are replaced, this is done by i) indicating the position of the replaced group by "des-terminology" as described above and ii) defining the replacing group. Thus -7'-desmethyl-7'-phenyl-MeBmt- is the residue of formula B above in which the terminal (8') methyl group is replaced by phenyl. 3'-Desoxy-3'-oxo-MeBmt- is the residue of formula B above in which the 3'-OH group is replaced by =O.

In addition, amino acid residues referred to by abbreviation, e.g. -Ala-, -MeVal-, -αAbu- etc... are, in accordance with conventional practice, to be understood as having the (L)-configuration unless otherwise indicated, e.g. as in the case of "-(D)Ala-". Residue abbreviations preceded by "Me" as in the case of "-MeLeu-", represent α-N-methylated residues. Individual residues of the cyclosporin molecule are numbered, as in the art, clockwise and starting with the residue -MeBmt-, -dihydro-MeBmt- etc. ... in position 1. The same numerical sequence is employed throughout the present specification and claims.]

Because of their unique pharmaceutical potential, the cyclosporins have attracted very considerable attention, not only in medical and academic circles, but also in the lay press. Cyclosporin itself is now commonly employed in the prevention of rejection following allogenic organ, e.g. heart, heart-lung, kidney and bone-marrow transplant, as well as, more recently, in the treatment of various auto-immune and related diseases and conditions. Extensive work has also been performed to investigate potential utility in the treatment of various parasitic diseases and infections, for example coccidiomycosis, malaria and schistosomiasis. Reports of investigative work into the potential utility of the very many other known cyclosporins in these or related indications now abound in the literature.

In accordance with the present invention it has now surprisingly been found that particular cyclosporins are useful in increasing sensitivity to other chemotherapy and, in particular, of effecting reversal of resistance, whether induced or inherent, to other chemotherapy.

Increased resistance to chemotherapeutic therapy following treatment over shorter or longer periods of time, generally following relatively prolonged chemotherapeutic medication, is a wide-spread phenomenon which has long been recognised and is widely documented in the art. The classic example is the increased or induced resistance of parasitic, in particular bacterial, viral or protozoal, organisms, following long-term or wide-spread medication employing individual drug-substances. In such instances the infecting organism becomes, with time, resistant to the drug substance to a greater or lesser degree and concomitantly difficult to combat or treat. An analogous phenomenon is observed in relation to the chemotherapeutic treatment of cancers, e.g. treatment of carcinomas, sarcomas or other tumors or malignant growths.

Chemotherapeutic treatment of cancers, e.g. by administration of drug substances, in particular anti-neoplastic or cytotoxic drugs, for example colchicine, etoposide, tenoposide, adriamycin, daunorubicin and vincristine, as a means of reducing, inhibiting or otherwise limiting tumor growth or metastasis, remains a first line approach to the treatment of cancers of various type. However it is commonly found that, while tumors may be susceptible to therapy initially, as treatment continues, resistance to such therapy develops, resulting in a decline in therapeutic efficacy. Where, as is common, in particular in the treatment of late-phase or terminal cancers, pleiotropic or multi-drug therapy is employed, multi-drug resistance commonly ensues. Analogous difficulties arise, e.g. in cases where particular forms of chemotherapeutic treatment have long been practiced and, for example, resistant strains of micro-organism arise which have developed an inherent or innate resistance. So too, particular forms of cancer or tumor are frequently encountered which exhibit an innate resistance to, or reduced level of sensitivity to, commonly employed anti-neoplastic or cytostatic drug therapy.

In accordance with the present invention it has been found that the cyclosporins hereinafter defined are useful in increasing sensitivity to, or increasing the efficacy of, chemotherapeutic drug therapy and, in particular, are useful in reversing chemotherapeutic drug resistance of varying types (e.g. acquired or innate), or in increasing or restoring sensitivity to administered drug therapy. Forms of chemotherapeutic drug therapy to which the present invention is applicable include, for example, anti-parasitic, e.g. anti-viral, anti-bacterial or anti-protozoal chemotherapy and, in particular, anti-neoplastic or cytostatic chemotherapy.

Cyclosporins suitable for use in accordance with the present invention are definable under various classes as follows.

CLASS 1

A cyclosporin wherein the 3'-carbon atom of the residue at the 1-position or the β-carbon atom of the residue at the 2-position is O-acyl or oxo substituted.

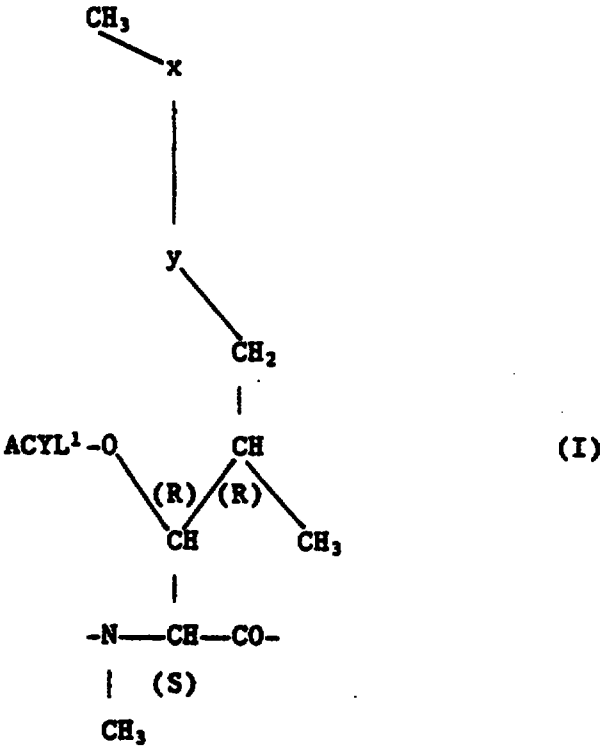
Preferred cyclosporins of this class are those:

1a) Wherein the 3'-carbon atom of the residue at the 1-position is O-acyl substituted.

When the 3'-carbon atom of the residue at the 1-position is O-acyl substituted, the residue at the 2-position may also be β-O-acylated.

A preferred group of cyclosporins of type 1a) are those:

1a[1]) Wherein the residue at the 1-position is a -3'-O-acyl-MeBmt- or -3'-O-acyl-dihydro-MeBmt- residue of formula I



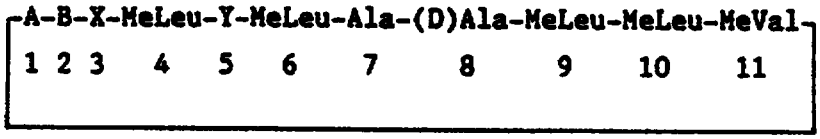
(I)

wherein -x-y- is $-CH_2-CH_2-$ or trans -CH=CH- and $ACYL^1$ represents an acyl group.

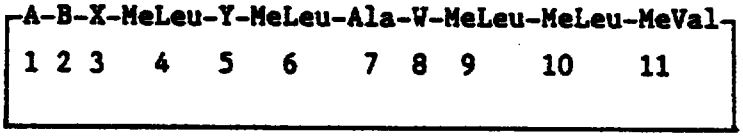
Suitable acyl groups as $ACYL^1$ in formula I, are those of formula R_1-CO- and R_2-O-CO- wherein R_1 is C_{1-4}alkyl or C_{1-4}azidoalkyl and R_2 is C_{1-4}alkyl, e.g. acetyl, 4-azidobutanoyl or methoxycarbonyl. Preferably $ACYL^1$ is a group of formula R_1-CO-, in which case R_1 is preferably C_{1-4}alkyl. Most preferably R_1-CO- is acetyl.

Alkyl groups as or comprising R_1 and R_2 may be branched or straight chain. Preferably they are straight chain. R_1 is most preferably methyl.

Especially preferred cyclosporins of group 1a[1] are those of the formula II or II'



(II)



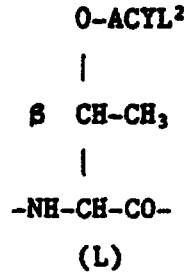
(II')

wherein

A is a residue as defined under 1a[1] above

B i s -αAbu-, -Thr-, -Val-, -Nva- or the residue of a β-O-acyl-α-amino acid,
X is -Sar- or the residue of an optically active, α-N-methylated α-amino acid residue having the (D)-configuration,
Y is -Val- or additionally, when B is -Nva-, -Nva-, and
W is the residue of a β-hydroxy- or β-O-acyl-α-amino acid having the (D)-configuration.

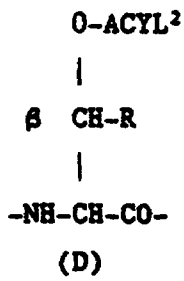
When B is a β-O-acyl-α-amino acid residue, this will generally have the (L) configuration. Suitably it is a residue of formula III



(III)

Wherein $ACYL^2$ represents an acyl group. Preferably it is an O-acyl-(L)-threonyl residue.

W is suitably -(D)Ser- or -(D)Thr- or O-acyl-(D)Ser- or O-acyl-(D)Thr- of formula III'



(III')

Wherein $ACYL^2$ has the meaning given for formula III and R is hydrogen or methyl.

Preferred acyl groups as $ACYL^2$ in formula III and III' are those of the formula R_3-CO- wherein R_3 is C_{1-4}alkyl. Alkyl groups as R_3 may be branched or straight chain. Preferably they are straight chain. Suitably $ACYL^2$ is acetyl.

When X in formula II is other than -Sar-, it is suitably -(D)Ala-.

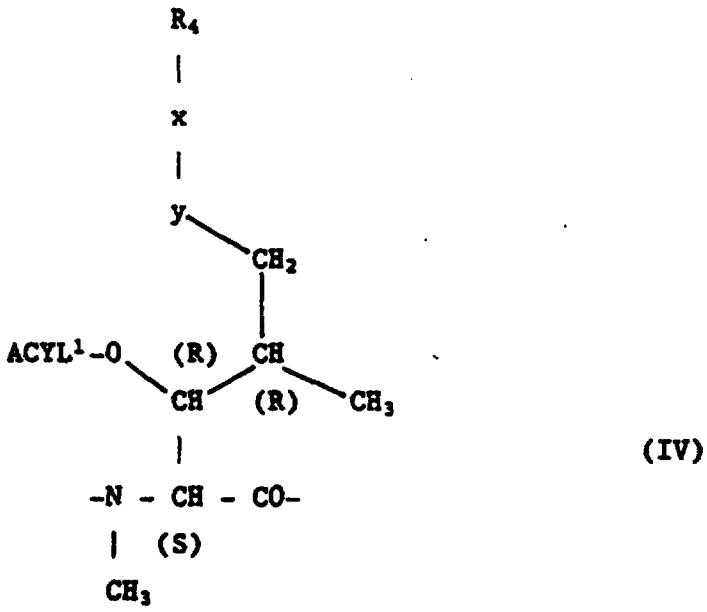
Examples of cyclosporins of this class suitable for use in accordance with the present invention are:

1.1 [3'-O-Acetyl-MeBmt]^1-Ciclosporin;
1.2 [3'-O-Acetyl-MeBmt]^1-[Val]^2-Ciclosporin;
1.3 [3'-O-Acetyl-MeBmt]^1-[Thr]^2-Ciclosporin;
1.4 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-Ciclosporin;
1.5 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-[Nva]^5-Ciclosporin;
1.6 [3'-O-Acetyl-MeBmt]^1-[(D)Ala]^3-Ciclosporin;
1.7 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-[(D)Ala]^3-Ciclosporin;
1.8 [3'-O-Acetyl-MeBmt]^1-[(D)MeVal]^{11}-Ciclosporin;
1.9 [3'-O-Acetyl-MeBmt]^1-[Val]^{11}-Ciclosporin;
1.10 [3'-O-Acetyl-dihydro-MeBmt]^1-Ciclosporin;
1.11 [3'-O-Methoxycarbonyl-MeBmt]^1-Ciclosporin;
1.12 [3'-O-(4-Azidobutanoyl)-MeBmt]^1-Ciclosporin;
1.13 [3'-O-Acetyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.14 [3'-O-Acetyl-N-desmethyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin; and
1.15 [3'-O-Acetyl-MeBmt]^1-[O-acetyl-(D)Ser]^8-Ciclosporin;

Preferred cyclosporins for use in accordance with the invention are cyclosporins 1.1 to 1.10 inclusive and 1.15 above and, most especially, cyclosporins 1.1, 1.2, 1.3, 1.4, 1.10 and 1.15.

A further group of cyclosporins of type 1a are those:

1a[2]) Wherein the residue at the 1-position is a -3'-O-acyl-8'-C_{1-8}alkoxy- -cis-MeBmt- or -dihydro-MeBmt-residue of the formula IV



(IV)

wherein
-x-y- is cis -CH=CH- or $-CH_2-CH_2-$, R_4 is C_{2-9}alkoxymethyl and $ACYL^1$ represents an acyl group.

Especially suitable as acyl groups in formula IV are those of formula R_5-CO- wherein R_5 is C_{1-4}alkyl.

Alkyl groups as R_5, as well as alkyl moieties comprising R_4, may be branched or straight chain. Preferably they are straight chain. Preferably R_4 is C_{2-5}alkoxymethyl. $ACYL^1$ in formula IV is suitably acetyl.

Especially preferred cyclosporins of group 1a[2] are those of formula II as illustrated above, wherein A is a residue of formula IV as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

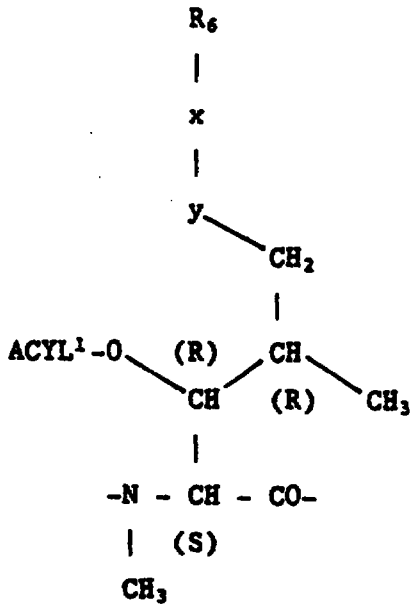
Examples of cyclosporins of group 1a[2], suitable for use in accordance with the present invention are:

1.16 [3'-O-acetyl-8'-methoxy-cis-MeBmt][1]-Ciclosporin;
1.17 [3'-O-acetyl-8'-t.butoxy-cis-MeBmt][1]-Ciclosporin;
1.18 [3'-O-acetyl-8'-methoxy-cis-MeBmt][1]-[O-acetyl-Thr][2]-Ciclosporin;
1.19 [3'-O-acetyl-8'-t.butoxy-cis-MeBmt][1]-[O-acetyl-Thr][2]-Ciclosporin;
1.20 [3'-O-acetyl-8'-methoxy-cis-MeBmt][1]-[Val][2]-Ciclosporin; and
1.21 [3'-O-acetyl-8'-methoxy-cis-MeBmt][1]-[Nva][2]-Ciclosporin;

A further group of cyclosporins of type 1a are those:

1a[3]) Wherein the residue at the 1-position is a -3'-O-acyl-cis-MeBmt-; a -3'-O-acyl-7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue, wherein the hydrocarbyl moiety comprises at least two carbon atoms; or a -3'-O-acyl-7'-desmethyl-7'-hydrocarbyl-dihydro-MeBmt- residue, wherein the hydrocarbyl moiety comprises at least two carbon atoms and wherein any aliphatic group or moiety present in said hydrocarbyl moiety is saturated.

These residues may be represented by the formula V



(V)

wherein
-x-y- is cis or trans -CH=CH- or $-CH_2-CH_2-$,
R_6 is hydrocarbyl and
$ACYL^1$ represents an acyl group,
with the proviso that, when -x-y- is trans -CH=CH- or $-CH_2-CH_2-$, R_6 comprises at least two carbon atoms (i.e. is other than methyl), and when -x-y- is $-CH_2-CH_2-$ any aliphatic group or moiety present as or in R_6 is saturated.

Especially suitable as acyl groups in formula V are those of formula R_5-CO- wherein R_5 is C_{1-4}alkyl, in particular acetyl.

Hydrocarbyl groups as R_6 include aromatic, aliphatic and araliphatic groups, whereby aliphatic groups and moieties may be branched or straight chain. Such groups may also bear further substituents such as halogen or hydroxy or may be unsubstituted.

Suitable hydrocarbyl groups as R_6 are alkyl, alkenyl, alkinyl, phenyl, phenylalkyl, phenylalkenyl and phenylalkinyl, especially alkyl, alkenyl and alkinyl groups containing maximally 20, preferably maximally 8 carbon atoms, and phenyl, phenylalkyl and phenylalkinyl groups containing maximally 12 carbon atoms.

Especially preferred groups R_6 are phenyl, phenyl-(C_{1-4}alkyl), C_{1-10}alkyl, C_{2-10}alkenyl and C_{2-10}alkinyl, especially phenyl, and C_{1-5}alkyl.

When -x-y- in formula V is $-CH_2-CH_2-$, hydrocarbyl groups as R_6 will include aromatic, saturated aliphatic and araliphatic groups in which the aliphatic moiety is saturated, e.g. including any such groups of this type as set forth above.

Especially preferred cyclosporins of this group are those of formula II as illustrated above, wherein A is a residue of formula V as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

Examples of cyclosporins of this group, suitable for use in accordance with the present invention are:

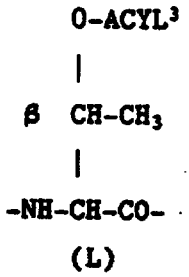
1.22 [3'-O-acetyl-7'-desmethyl-7'-phenyl-MeBmt]^1-Ciclosporin;
1.23 [3'-O-acetyl-cis-MeBmt]^1-Ciclosporin;
1.24 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin;
1.25 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.26 [3'-O-acetyl-7'-desmethyl-7'-i. pentyl-cis-MeBmt]^1-Ciclosporin;
1.27 [3'-O-acetyl-7'-desmethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin;
1.28 [3'-O-acetyl-7'-desmethyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporin;
1.29 [3'-O-acetyl-7'-desmethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin;
1.30 [3'-O-acetyl-7'-desmethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin;
1.31 [3'-O-acetyl-7'-desmethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
1.32 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
1.33 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin; and

1.34 [3'-O-acetyl-7'-desmethyl-7'-(3-bromo-n.propyl)-cis-MeBmt]^1-Ciclosporin;

A further group of cyclosporins of CLASS 1 are those:

1b) Wherein the β-carbon atom of the residue at the 2-position is O-acyl substituted, i.e. wherein the residue at the 2-position is a β-O-acyl-α-amino acid residue, and the residue at the 1-position is other than as defined under 1a) above.

When the residue at the 2-position is a β-O-acyl-α-amino acid residue, this residue will generally have the (L) configuration. Suitably it is a residue of formula III''



(III'')

in which ACYL^3 represents an acyl group. Preferably it is an O-acyl-(L)-threonyl residue.

Suitable groups as ACYL^3 in formula III'', are those of the formula R_3-CO- or R_7-CO-R_8-CO-, wherein R_3 has the meanings given for formula III, R_7 is the residue of a cyclosporin having a β-oxy-(L)-α-amino acid residue in the 2-position attached to the moiety -CO-R_8-CO- via the β-oxygen atom of said residue, and R_8 is C_{1-8}alkylene.

Alkylene groups as R_8 may be branched or straight chain. Preferably they are straight chain. R_8 is preferably C_{1-4}alkylene. Acyl groups of formula R_3-CO- are generally preferred, preferred significances for R_3-CO- being as hereinbefore set forth in relation to formula III.

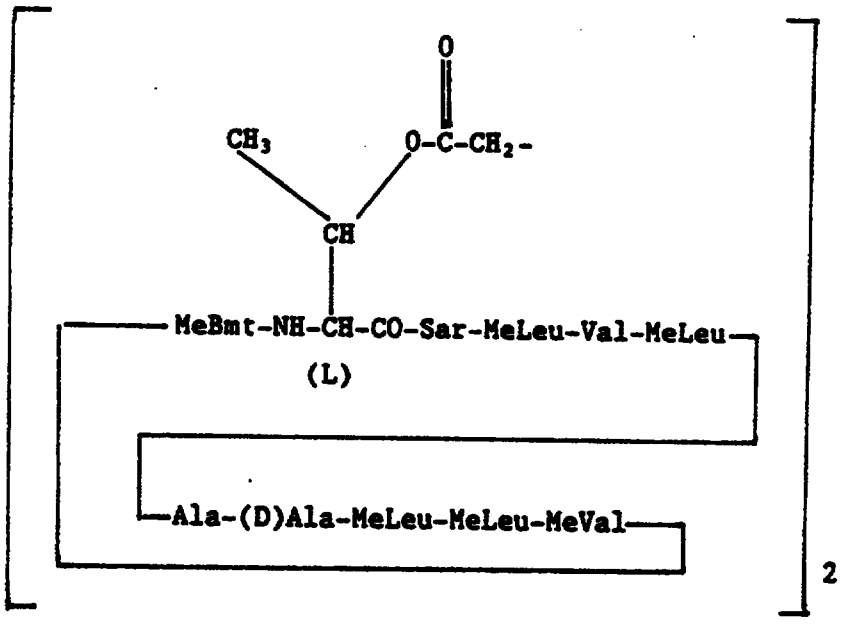
Particular cyclosporins of this group are those of formula II as illustrated above, wherein A is -MeBmt- or -dihydro-MeBmt-, B is a residue as defined under 1b above, e.g. of formula III'' as defined above, X is -Sar- and Y is -Val-.

Examples of such cyclosporins suitable for use in accordance with the present invention are:

1.35 [O-Acetyl-Thr]^2-Ciclosporin; and

1.36 1,2-Ethanedicarboxylic acid [O-threonyl]^2-Ciclosporin di-ester.

Ciclosporin 1.36 has the formula VI

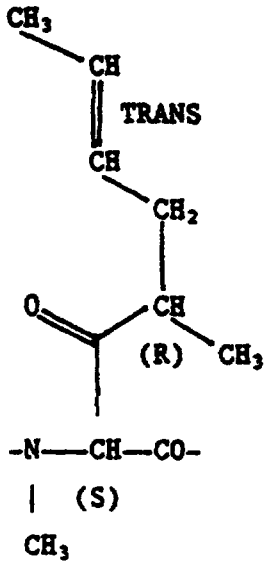


(VI)

A further preferred group of cyclosporins of CLASS 1 are those:

1c) Wherein the 3'-carbon atom of the residue at the 1-position is oxo substituted.

When the 3'-carbon atom of the residue at the 1-position is oxo substituted this is suitably -3'-desoxy-3'-oxo-MeBmt- of formula VII



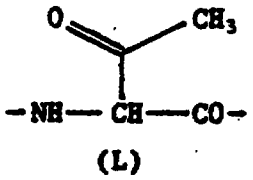
(VII)

Especially preferred cyclosporins of this group are those of formula II as illustrated above, wherein A is a residue of formula VII above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

A yet further group of cyclosporins of CLASS I are those:

1d) Wherein the β-carbon atom of the residue at the 2-position is β-oxo substituted, i.e. wherein the residue at the 2-position is a β-oxo-α-amino acid residue.

When the residue at the 2-position is a β-oxo-α-amino acid residue, this residue will generally have the (L) configuration. Suitably it is -α-methylketo-Gly- of formula VIII



(VIII)

Examples of cyclosporins belonging to groups 1c and 1d, suitable for use in accordance with the present invention are:

1.37 [3'-Desoxy-3'-oxo-MeBmt]^1-Ciclosporin;
1.38 [3'-Desoxy-3'-oxo-MeBmt]^1-[Val]^2-Ciclosporin;
1.39 [3'-Desoxy-3'-oxo-MeBmt]^1-[Nva]^2-Ciclosporin;
1.40 [α-Methylketo-Gly]^2-Ciclosporin; and
1.41 [Dihydro-MeBmt]^1-[α-methylketo-Gly]^2-Ciclosporin;

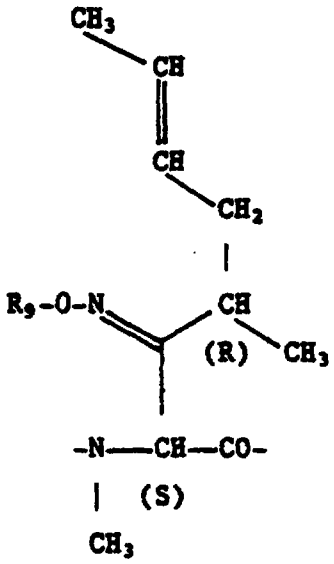
Cyclosporins 1.37 to 1.39 are especially preferred.

CLASS 2

A cyclosporin wherein:

i) The 3'-carbon atom of the residue at the 1-position is C_{1-4}alkoxyimino substituted, e.g. a cyclosporin wherein the residue at the 1 position is a -3'-desoxy-3'-(C_{1-4}alkoxyamino)-MeBmt- residue; or
ii) The residue at the 2-position is an (L)-isoleucyl residue; or
iii) The residue at the 11-position is an N-methyl-(L)-alanyl, N-methyl-(L)-isoleucyl or N-methyl-(L)-alloisoleucyl or N-methyl-(L)-leucyl residue.

-3'-Desoxy-3'-(C_{1-4}alkoxyimino)-MeBmt- residues as defined under (i) above have the formula IX

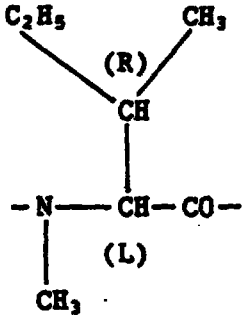


(IX)

Wherein R_9 is C_{1-4}alkyl.

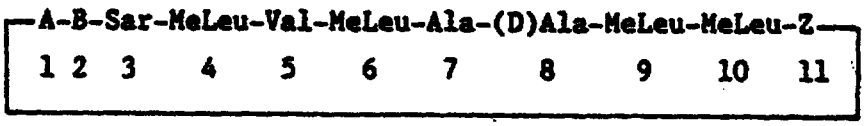
Alkyl groups as R_9 may be branched or straight chain. Preferably they are straight chain.

By N-methyl-(L)-alloisoleucyl (-Meallolle-) as used under (iii) above is meant the residue of formula X



(X)

Preferred cyclosporins of this class are those of formula XI



(XI)

wherein

A is -MeBmt-, -dihydro-MeBmt- or a residue as defined under (i) above,

B is -αAbu-, -Thr-, -Val- or -Nva- or additionally, when A is -MeBmt-or -dihydro-MeBmt-, -Ile-, and

when

A is -MeBmt- or -dihydro-MeBmt- and

B is -αAbu-, -Thr-, -Val- or -Nva-,

Z is -MeAla-, Melle-, Meallolle- or -MeLeu-, or

when

A is a residue as defined under (i) above or

when

B is -Ile-,

Z is -MeVal-.

Examples of such cyclosporins suitable for use in accordance with the present invention are:

2.1 [3'-Desoxy-3'-methoxyimino-MeBmt]^{1}-Ciclosporin;

2.2 [Ile]^{2}-Ciclosporin;

2.3 [MeAla]^{11}-Ciclosporin;

2.4 [MeIle]^{11}-Ciclosporin; and

2.5 [MeAlloIle]^{11}-Ciclosporin; and

2.6 [MeLeu]^{11}-Ciclosporin;

Of this class, cyclosporins wherein the residue at the 2-position has the meaning given under (ii) above, especially cyclosporin 2.2, are preferred.

Cyclosporins wherein the residue at the 11-position has the meaning given under (iii) above, e.g. cyclosporins 2.4 and 2.5, are also of particular interest.

CLASS 3

Cyclosporins of formula XI as illustrated above wherein:

Z is -Val- or -MeVal-:

when

Z is -Val-,

A is -MeBmt- or -dihydro-MeBmt-; or

when

Z is -MeVal-

A is -3'-desoxy-MeBmt-, 3'-desoxy-dihydro-MeBmt-, -N-desmethyl-MeBmt-, -N-desmethyl-dihydro-MeBmt-, -3'-desoxy-4'-desmethyl-dihydro-MeBmt- or -MeLeu-: and

when

Z is -Val-,

B is -αAbu- or -Thr-;

when

Z is -MeVal- and

A is -3'-desoxy-MeBmt-, -3'-desoxy-dihydro-MeBmt-, -3'-desoxy-4'-desmethyl-dihydro-MeBmt- or -MeLeu-,

B is -αAbu-; or

when

Z is -MeVal- and

A is -N-desmethyl-MeBmt- or -N-desmethyl-dihydro-MeBmt-,

B is -Thr-.

Cyclosporins of this class are:

3.1. [Val]^{11}-Ciclosporin (also known as cyclosporin E);

3.2. [Dihydro-MeBmt]^{1}-[Val]^{11}-Ciclosporin (or dihydrocyclosporin E);

3.3 [3'-Desoxy-MeBmt]^{1}-Ciclosporin (or cyclosporin F);

3.4 [3'-Desoxy-dihydro-MeBmt]^{1}-Ciclosporin (or dihydrocyclosporin F);

3.5 [N-Desmethyl-MeBmt]^{1}-[Thr]^{2}-Ciclosporin (or cyclosporin P);

3.6 [N-Desmethyl-dihydro-MeBmt]^{1}-[Thr]^{2}-Ciclosporin (or dihydrocyclosporin P);

3.7 [Thr]^{2}-[Val]^{11}-Ciclosporin (or cyclosporin W);

3.8 [Dihydro-MeBmt]^{1}-[Thr]^{2}-[Val]^{11}-Ciclosporin (or dihydrocyclosporin W);

3.9 [3'-Desoxy-4'-desmethyl-dihydro-MeBmt]^{1}-Ciclosporin (or cyclosporin Z);

3.10. [MeLeu]^{1}-Ciclosporin (or cyclosporin 28).

Various acylated cyclosporins of group 1a), in particular group 1a^{1}), and group 1b) are known. Thus cyclosporins 1.1, 1.4, 1.8, 1.9, 1.13, 1.14 and 1.35 are known from and are described, together with processes for their production, e.g. from Traber et al., Helv. Chim. Acta, 60, 1247 et seq. (1977), 65, 1655 et seq. (1982), 70, 13 et seq. (1987); Kobel et al., Europ. J. Applied Microbiology, Biotechnology, 14, 273 et seq. (1982); and von Wartburg et al., Progress in Allergy, 38, 28 et seq. (1986).

Cyclosporins 1.3, 1.5, 1.6, 1.7 and 1.10 are new and form part of the present invention as novel compounds per se.. Cyclosporins 1.2, 1.5 to 1.7 and 1.10 may be prepared analogously to the methods described in the art, e.g. for the preparation of cyclosporin 1.1., by acetylation of the corresponding cyclosporins wherein the residue at the 1-position is -MeBmt- or -dihydro-MeBmt-. The cyclosporin starting materials are known, in the case of cyclosporins 1.6 and 1.7 from e.g. European patent publication no. 0 194 972. The product cyclosporins have the following physical characteristics:

	Physical data:
1.2	$[\alpha]_D^{20}$= -328° (c=0.97 in $CHCl_3$)
1.5	$[\alpha]_D^{20}$= -250° (c=1.0 in $CHCl_3$)
1.6	$[\alpha]_D^{20}$= -302.6° (c=0.5 in $CHCl_3$)
1.7	$[\alpha]_D^{20}$= -296.2° (c=0.5 in $CHCl_3$)
1.10	$[\alpha]_D^{20}$= -293° (c=0.55 in $CHCl_3$)

In general, when the residue at the 2-position in the cyclosporin starting material is a β-hydroxy-α-amino acid residue, for example -Thr-, the β-OH group at this position will be more readily susceptible to reaction than the 3'-hydroxy, e.g. of -MeBmt- or -dihydro-MeBmt-, at the 1-position. Cyclosporins wherein the residue at the 2-position, but not the residue at the 1-position, is acylated [as in the case of group 1b) cyclosporins, for example cyclosporin 1.35] or wherein both the residue at the 1- and 2-position is acylated [as in the case of cyclosporins 1.13 and 1.14 of group 1a[1]] may thus be readily obtained, according to, or analogously to, the methods described in the art, taking advantage of this relative difference in reactivity. To produce cyclosporins wherein the 1-position is 3'-O-acylated but having a free β-OH group at 2-position [as in the case of cyclosporin 1.3] it is first necessary to protect the hydroxy group at the 2-position and then remove the protecting group subsequent to acylation of the residue at the 1-position. The following example is illustrative of the general procedure:

EXAMPLE A

Preparation of [3'-O-acetyl-MeBmt]^1-[Thr]^2-Ciclosporin (Cyclosporin 1.3):

Step 1: introduction of an O-protecting group at -Thr^2 of [Thr]^2-Ciclosporin

6.09g of [Thr]^2-Ciclosporin are dissolved in 25 ml abs. CH_2Cl_2 and 5ml ethinyl-ether and 0.2ml trifluoroacetic acid are added. The reaction mixture is stirred for 20 hrs. at room temperature under an atmosphere of nitrogen. The reaction mixture is shaken with cold, 20% $KHCO_3$, washed with water, extracted with CH_2Cl_2, dried over Mg_2SO_4, filtered and evaporated. The obtained foam is purified chromatographically using 440g silica gel (0.04-0.06) using toluene/acetone (2:1) as eluant and collecting in 500ml fractions. The product, [Thr-1-methyl-ethoxymethyl ether]^2-Ciclosporin is recovered from fractions 26 to 29: m.p. = 76.6°.

Step 2: acylation of [Thr]^2-Ciclosporin in -Thr^2 O-protected form

10.66g of the product of step 1, 106 ml acetic acid anhydride and 1.22g of 4-dimethylaminopyridine are combined and stirred for 20 hrs. at room temperature and taken up with toluene at 40°C. The residue is dissolved in 400ml toluene and extracted 1x with 250 ml cold acetic acid, 1x with 250 ml H_2O, 1x with 200ml cold 20% $KHCO_3$ and 1x with 250ml H_2O. The toluene extracts are dried over $MgSO_4$, filtered evaporated and dried under vacuum to yield [3'-O-acetyl-MeBmt]^1-[Thr-1-methyl-ethoxymethyl ether]^2-Ciclosporin.

Step 3: deprotection of [3'-O-acetyl-MeBmt]^1-[Thr]^2-Ciclosporin in -Thr-^{2} O-protected form

11.38g of the product of step 2, 80ml tetrahydrofuran and 160ml 67% acetic acid are stirred for 48 hrs. at room temperature under N_2. The reaction mixture is taken up in toluene, the residue dissolved in toluene, shaken with 20% $KHCO_3$, washed with H_2O and the toluene extracts dried over $MgSO_4$ and filtered. The filtrate is evaporated and purified chromatographically using 440g silica gel (0.04-0.06) using toluene/acetone (3:1) as eluant and collecting in 500ml fractions. The end-product, [3'-O-acetyl-MeBmt]^1-[Thr]^2-Ciclosporin is recovered from fractions 5-9: m.p. = 75.6°, $[\alpha]_D^{20}$ = -275.5° (c = 0.65 in $CHCl_3$).

Cyclosporins of formula II' are new and form part of the present invention as novel compounds per se. Accordingly in a further aspect the present invention provides, as a novel group of cyclosporins, those:

1a^4) Of the formula II' as hereinbefore defined.

Cyclosporins of group 1a^4) may be prepared entirely analogously to the procedures for the production of known cyclosporins 1.1, 1.4 etc., hereinbefore referred to or analogously to the production of cyclosporin 1.3, starting from the corresponding cyclosporins wherein the residue at the 1-position is -MeBmt- or -dihydro-MeBmt. Required starting materials are known and described, together with the methods for their production, e.g. in UK patent application no. 2 155 936, US patent no. 4 639 434 and European patent publication no. 0 056 782. As indicated above, cyclosporins of formula II', wherein W is the residue of a β-hydroxy- (rather than β-O-acyl-) -α-amino acid residue are prepared analogously e.g. to example A, by first protecting at the 8-position, acylating at the 1-position and then de-protecting at the 8-position.

Cyclosporin 1.15 of group 1a^4) has the following characterising data:
$[\alpha]_D^{20}$ = -272° (c = 1.0 in $CHCl_3$).

Cyclosporins wherein the 3'-carbon atom of the residue at the 1-position is azidoalkylcarbonyloxy or alkoxycarbonyloxy substituted are also new and form part of the present invention as novel compounds per se.

A group of cyclosporins of this type comprises those:

1a^5) Wherein the residue at the 1-position is a -3'-O-(C_{1-4}azidoalkyl)-carbonyl- or -3'-O-(C_{1-4}alkoxy)-carbonyl- -MeBmt- or -dihydro-MeBmt- residue, i.e. of formula I as illustrated above, wherein ACYL^1 is a group of formula R_1'-CO- or R_2-O-CO- wherein R_1' is C_{1-4}azidoalkyl and R_2 is C_{1-4}alkyl.

Preferred cyclosporins of this group are those of formula II as illustrated above, wherein A is a residue as defined under 1a^5 above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

The present invention also provides a process for the production of cyclosporins of group 1a^5) which process comprises:

a) reacting the corresponding cyclosporin wherein the residue at the 1-position is -MeBmt- or -dihydro-MeBmt- with a compound of formula XII or XIII.

R_1'-CO-Q (XII)

R_2-O-CO-Q (XIII)

Wherein R_1' and R_2 have the meanings given above and Q is a leaving group.

Q is suitably halogen or -OH. When Q is halogen, reaction is suitably carried out e.g. in the presence of a catalyst such as n-butyllithium. When Q is -OH reaction is suitably carried out in the presence of an activating agent. Reaction is suitably performed at temperatures of from ca. -100 to -50°C, e.g. as described in the following examples B:

EXAMPLES B

1. Preparation of [3'-O-methoxycarbonyl-MeBmt]^1-Ciclosporin (cyclosporin 1.11)

3.76ml of a 1.48M solution of n-butyllithium in 3.76ml hexane are added to 0.87ml diisopropylamine in tetrahydrofuran at -78° and the whole stirred for 30 min. at -78°C. 1.0g Ciclosporin in 15ml dry tetrahydrofuran are added at the same temperature and stirring continued for a further 30 min.. 0.326ml methylchloroformate are added and stirring continued for a further 1 hour at -78°C. The temperature is then allowed to rise to room temperature. 10ml of water are added and most of the tetrahydrofuran removed by evaporation. The residue is taken up in 100ml ethyl ether and 50ml water, the aqueous layer separated and extracted 2x with ethyl ether. The combined organic extracts are dried over $MgSO_4$ and evaporated to dryness. The residue is purified chromatographically on silica gel, eluting with ethyl acetate, to yield the title compound:
$[\alpha]_D^{20}$ = - 234° (c = 1.0 in $CHCl_3$).

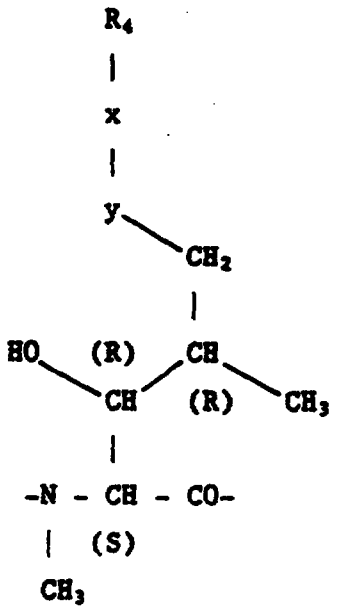
2. Preparation of [3'-O-(4-azidobutanoyl)-MeBmt]^1-Ciclosporin (cyclosporin 1.12)

7.74g γ-azidobutyric acid, 8.6g 4-dimethylaminopyridine and 5.11g Mullayama-reagent (2-chloro-1-methyl-pyridinium iodide) are added to 12.02g Ciclosporin in 200ml abs. CH_2Cl_2, and the reaction mixture is stirred for 90 hrs. at room temperature. The obtained product is diluted with CH_2Cl_2 shaken with 100ml ice-cold, 10% NaOH, 200ml H_2O and 200ml 10% acetic acid washed with water, and the organic phases are dried over Na_2SO_4. The filtrate is evaporated and dried again. The product is purified chromatographically using 1.2kg silica gel (0.04-0.06mm) using hexane/acetone (3:1) as eluant collecting in fractions of 250ml up to fraction 20 and then hexane/acetone (7:3), collecting in fractions of 300ml thereafter. The title compound is recovered from fractions 23-27: $[\alpha]_D^{20}$ = -289.8° (c= 0.5 in $CHCl_3$).

Cyclosporins of group 1a^2 as hereinbefore set forth are also new and form part of the present invention as novel compounds per se.

The present invention also provides a process for the production of cyclosporins of group 1a^2) which process comprises:

b) acylating the corresponding cyclosporin wherein the residue at the 1-position is an -8'-C_{1-8}alkoxy-cis-MeBmt- or -8'-C_{1-8}alkoxy-dihydro-MeBmt- residue of formula XIV



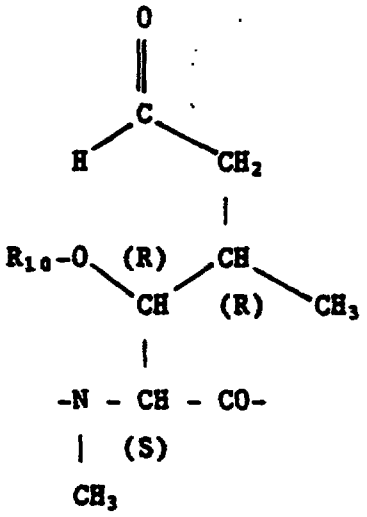
(XIV)

wherein -x-y- and R_4 have the meanings given above for formula IV, for example acylating a cyclosporin of formula II as illustrated above wherein A is a residue of formula XIV as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-, e.g. by reaction with a compound of formula XV

R_5-CO-Q (XV)

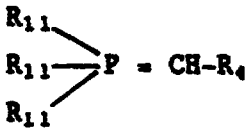
wherein R_5 is C_{1-4}alkyl and Q is a leaving group, for example a halogen atom; or

c) for the preparation of a cyclosporin of group 1a^2 wherein the residue at the 1-position is a -3'-O-acyl-8'-C_{1-8}alkoxy-cis-MeBmt- residue of formula IV as illustrated above, wherein -x-y- is cis -CH=CH-, R_4 has the meaning given for formula IV and ACYL^1 is an acyl O-protecting group, for example acetyl, reacting a cyclosporin wherein the residue at the 1-position is a -3'-O-acyl-5'-des-(1-propenyl)-5'-formyl-MeBmt- residue of formula XVI



(XVI)

wherein R_{10} is an acyl O-protecting group, e.g. acetyl, for example a cyclosporin of formula II as illustrated above wherein A is a residue of formula XVI as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-, with a compound of formula XVII



(XVII)

wherein each R_{11} is phenyl or C_{1-4}alkyl and R_4 has the meaning given for formula IV.

Reaction in accordance with process step (c) above may be carried out in accordance with standard methods employed for effecting a Wittig reaction, e.g. under anhydrous conditions, for example in an inert solvent or diluent such as absolute benzene, teterahydrofuran, ethyl-ether or toluene, at a temperature of from about -80 °C to 20 °C, optionally in the presence of a salt, e.g. an alkali-metal halogenide. The reaction is suitably carried out under an inert atmosphere.

The cyclosporin starting materials required for process step (c) may be obtained from the corresponding cyclosporins wherein the residue at the 1-position is -3'-O-acyl-protected-MeBmt-, for example -3'-O-acetyl-MeBmt- by:

d) ozonolysation and treatment of the immediately obtained ozonolysis product with a mild reducing agent.

Ozonolysis in accordance with the reaction step (d) may be carried out in accordance with standard techniques, e.g. in an ozonisor in the presence of, e.g. ethyl acetate or dichloromethane, at a temperature of from about -90 to about -40 °C. A suitable mild reducing agent is dimethyl sulfide. Suitably, ozonolysis and treatment with the mild reducing agent is carried out in a single reaction vessel, e.g. as described in the following examples C.

The starting materials for process step (d) are cyclosporins of group 1a[1] and are known or may be obtained as hereinbefore described.

Process step (b) may be carried out analogously to processes for the production of cyclosporins of group 1a[1]) and 1b) as hereinbefore described, e.g. with reference to the literature. Similarly cyclosporins of group 1a[2]) having a free β-hydroxy-α-amino acid residue, e.g. -Thr-, at the 2-position may be produced by intermediate protection and subsequent deprotection of the β-OH group, e.g. proceeding analogously to the methods described in relation to example A above. The starting materials for process step (b) above may be obtained by:

e) deprotection of the corresponding cyclosporin wherein the residue at the 1-position is an -8'-C_{1-8}alkoxy-cis-MeBmt- or -8'-C_{1-8}alkoxy-dihydro-MeBmt- residue in 3'-O-protected form; or

f) reduction of the corresponding cyclosporin wherein the residue at the 1-position is an -8'-C_{1-8}alkoxy-cis-MeBmt- residue in free or 3'-O-protected form and, when required, carrying out process step (e).

Suitable 3'-O-protecting groups in the starting materials for process step (e) include any of those known and commonly employed in the art of peptide chemistry including acyl and ether protecting groups. The starting materials for process step (e) thus include the products of process step (c) hereinbefore described. Corresponding starting materials wherein the 3'-O-protecting group is other than acyl may be obtained analogously to process steps (d) and (c) starting from the appropriate 3'-O-protected cyclosporins.

Process step (e) itself can be carried out in accordance with procedures commonly employed in the art of peptide chemistry, e.g. by hydrolysis in the presence of a base such as an alkali metal alkoxide or carbonate to remove acetyl protecting groups or hydrolytic ether cleavage, e.g. in the presence of trifluoroacetic acid or HCl to remove protecting ether groups. Process step (e) is suitably conducted at temperatures of from about -20 to about 20 °C, e.g. as hereinafter described in examples D.

Process step (f) may also be carried out analogously to known methods, e.g. for reducing naturally occuring cyclosporins to the corresponding dihydrocyclosporins, for example by catalytic hydrogenation, e.g. in accordance with the general methods disclosed in U.K. Patent Specification No. 1 567 201. Hydrogenation is suitably effected under neutral pH conditions at temperatures of from about 20° to about 30 °C and at atmospheric or slightly elevated pressure, in the presence of a catalyst such as platinum or, preferably, paladium (e.g. paladium on charcoal) in the presence of an inert solvent or diluent such as ethyl acetate or lower aliphatic alkanols such as methanol and isopropanol.

The cyclosporin starting materials for process step (b) are also new and form part of the present invention as novel compounds per se. In a further aspect the present invention accordingly also provides:

CLASS 4

A cyclosporin wherein the residue at the 1-position is an -8'-alkoxy-cis-MeBmt- or -8'-C_{1-8}alkoxy-dihydro-MeBmt- residue of formula XIV as defined above.

Preferred cyclosporins of this class are those of formula II as defined for process step (b).

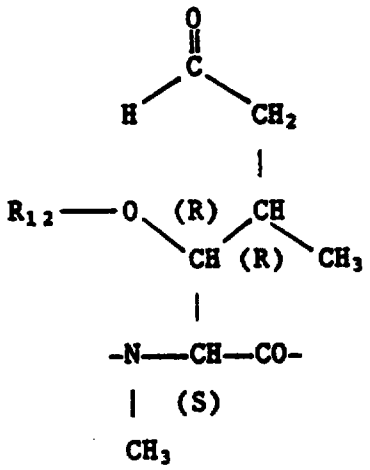
In addition to their utility as intermediates, cyclosporins of class 4 also possess, e.g. immunosuppressive, anti-inflammatory and anti-parasitic activity as hereinafter described. The said cyclosporins thus have utility in their own right.

Cyclosporins of class 4 also exhibit activity in increasing sensititvity to, or increasing the efficacy of, chemotherapeutic drug therapy and, in particular in reversing chemotherapeutic drug resistance, e.g. resistance to anti-neoplastic or cytostatic chemotherapy, as herein disclosed for cyclosporins of classes 1 to 3. Having regard e.g. to their inherent immunosuppressive properties however, cyclosporins of class 4 are generally less suitable for use in such indications.

The cyclosporin starting materials for process step (c) are also new and form part of the present invention as novel compounds per se. These starting materials may, of course, be subjected to intervening de-protection and/or re-protection, e.g. for the purposes of handling, transport or storage, in accordance with methods known or practiced in the art. In a yet further aspect the present invention accordingly also provides:

CLASS 5

A cyclosporin wherein the residue at the 1-position is -5'-des-(1-propenyl)-5'-formyl-MeBmt- in free or in 3'-O-protected form, i.e. a residue of formula XVIII

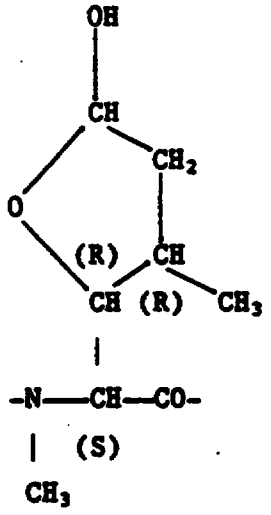


(XVIII)

wherein R_{12} is hydrogen or an O-protecting group.

Preferred protecting groups as R_{12} are acyl O-protecting groups, e.g. acetyl. Preferred cyclosporins of this class are those of the formula II as illustrated above, wherein A is a residue of formula XVIII as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

When R_{12} is hydrogen, the residue of formula XVIII also exists in the cyclic tautomeric form of formula XVIII':



(XVIII')

Such tautomers are to be understood as being within the purview of the present invention, e.g. embraced by the definition for class 5 cyclosporins above.

The following examples are illustrative of the above processes for the preparation of cyclosporins of group $1a^2$ and of classes 4 and 5.

EXAMPLES C

Preparation of cyclosporins of group $1a^2$.

Preparation of [3'-O-acetyl-8'-methoxy-cis-MeBmt]^1-Ciclosporin(cyclosporin 1.16):

16g Methoxymethyltriphenylphosphoniumbromide are suspended in 270ml absolute tetrahydrofuran (THF) in argon and cooled to -75°C. A solution of 5g potassium t.butylate in 200ml absolute THF is added dropwise over 30 minutes and the mixture is stirred again. After 2 hours a solution of 10g of [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-Ciclosporin in 25ml THF is added dropwise over 20 minutes. The

mixture is stirred for 4 hours at room temperature, then treated with 400ml ethyl acetate. The extracts are washed with 2N HCl solution, saturated $NaHCO_3$ and saturated brine. The concentrated filtrate is chromatographed on 1.2kg and 0.44kg silica gel (0.04 to 0.063mm) with $CHCl_3$ (10-40%) acetone/ethyl acetate to give the title compound: $[\alpha]_D^{20}$ = -267° (c = 0.53 in $CHCl_3$).

Cyclosporins 1.17 to 1.21 may be prepared analogously. These have the following physical characteristics:

	Physical data:
1.17	$[\alpha]_D^{20}$ = -283° (c= 0.544 in $CHCl_3$)
1.18	$[\alpha]_D^{20}$ = -209.1° (c= 0.605 in $CHCl_3$)
1.19	$[\alpha]_D^{20}$ = -282.96° (c= 0.405 in $CHCl_3$)
1.20	$[\alpha]_D^{20}$ = -268° (c= 0.615 in $CHCl_3$)
1.21	$[\alpha]_D^{20}$ = -248.7° (c= 0.65 in $CHCl_3$)

The starting material for the above process, which is a cyclosporin of class 5, is produced as follows:

Production of [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-Ciclosporin (cyclosporin 5.1):

48.5g of [3'-O-acetyl-MeBmt]^1-Ciclosporin in 70ml ethyl acetate are ozonised for 45 mins. at -70°C, using a Fischer ozone generator at 0.4 atm. with a current flow of 110 l/h. The obtained solution is gassed with N_2 and 9.8ml dimethylsulfide are added. The solution is stirred for 2 hrs. at room temperature, concentrated by evaporation, washed 2x with benzene and dried under high vacuum to yield the desired product. This is used directly for further reaction without further purification: $[\alpha]_D^{20}$ = -302° (c = 1.15 in $CHCl_3$).

The following cyclosporins are obtained analogously

5.2 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[O-acetyl -Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -272.6° (c= 0.504 in $CHCl_3$), m.p. = 156-160°

5.3 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -306° (c=1.03 in $CHCl_3$), m.p. = 168-170°

5.4 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Nva]^2-Ciclosporin: $[\alpha]_D^{20}$ = -291.76° (c= 0.51 in $CHCl_3$).

EXAMPLES D

Preparation of cyclosporins of class 4.

Preparation of [8'-methoxy-cis-MeBmt]^1-Ciclosporin (cyclosporin 4.1):

4g of cyclosporin 1.16 (from examples C) in 41ml methanol/water (5:1) are heated with 3.5g potassium carbonate and stirred at room temperature. After 21 hours the cooled solution is made acid with 10% tartaric acid solution and extracted three times with $CHCl_3$. The extracts are washed with saturated $NaHCO_3$ and water and dried over Na_2SO_4 and concentrated. Chromatography on 220g silica gel with ethyl acetate and ethyl acetate/hexane (100 to 20%) gives the title compound: $[\alpha]_D^{20}$ = -239° (c = 0.53 in $CHCl_3$).
The following cyclosporins are obtained analogously:

4.2 [8'-t.-Butoxy-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -228° (c = 0.5 in $CHCl_3$);
4.3 [8'-Methoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -220° (c = 0.37 in $CHCl_3$);
4.4 [8'-t.-Butoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -221° (c = 0.43 in $CHCl_3$);
4.5 [8'-Methoxy-cis-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -241° (c = 0.54 in $CHCl_3$);
4.6 [8'-Methoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporin: $[\alpha]_D^{20}$ = -236° (c = 0.634 in $CHCl_3$);

Production of [8'-methoxy-dihydro-MeBmt]^1-Ciclosporin (cyclosporin 4.7).

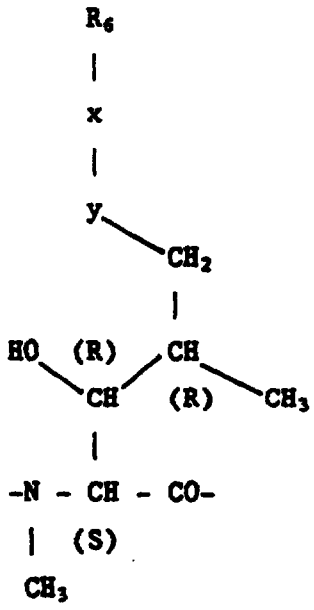
302mg of cyclosporin 4.1 are dissolved in 10ml abs. ethanol and hydrogenated at room temperature and atmosperic pressure over 5% Pd on charcoal. After the uptake of the theoretical amount of hydrogen (50 min.), the catalyst is separated by filtration over hyflo, and the solvent evaporated at reduced pressure. The residue is chromatographed on 70g silica gel (O = 0.015mm) with hexane-acetone (1:1) yielding the title compound: $[\alpha]_D^{20}$ = -229° (c = 0.52 in $CHCl_3$).

The following cyclosporins are obtained analogously:
4.8 [8'-Methoxy-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -217.5° (c = 0.32 in $CHCl_3$);
4.9 [8'-Methoxy-dihydro-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -223.6° (c = 0.58 in $CHCl_3$);
4.10 [8'-Methoxy-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin: $[\alpha]_D^{20}$ = -221.5° (c = 0.594 in $CHCl_3$);

Cyclosporins of group 1a^3 as hereinbefore set forth are also new and form part of the present invention as novel compounds per se.

The present invention also provides a process for the production of cyclosporins of group 1a^3, which process comprises:

g) acylating the corresponding cyclosporin wherein the residue at the 1-position is -cis-MeBmt-; a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms; or a -7'-desmethyl-7'-hydrocarbyl-dihydro-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms and wherein any aliphatic group or moiety present as or in said hydrocarbyl moiety is saturated, which residue may be represented by the formula XIX

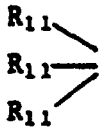


(XIX)

wherein -x-y- and R_6 have the meanings given above for formula V, for example, acylating a cyclosporin of formula II as illustrated above wherein A is a residue of formula XIX as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-, e.g. by reaction with a compound of formula XV as defined above; or

h) for the preparation of a cyclosporin of group 1a^3 wherein the residue at the 1-position is -3'-O-acyl-cis-MeBmt-whereinthe acyl moiety is an acyl O-protecting group, or a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms and wherein the O-acyl moiety is an acyl O-protecting group, which residue may be represented by the formula V as illustrated above wherein -x-y- is cis or trans -CH=CH-, R_6 has the meaning given for formula V and ACYL^1 is an acyl O-protecting group, for example acetyl, reacting a cyclosporin wherein

the residue at the 1-position is a 3'-O-acyl-5'-des-(1-propenyl)-5'-formyl-MeBmt- residue of formula XVI as defined above, for example a cyclosporin of formula II as illustrated above, wherein A is a residue of formula XVI as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-, with a compound of formula XX



(XX)

Wherein each R_{11} is phenyl or C_{1-4}alkyl and R_6' is hydrocarbyl of at least 2 carbon atoms and, when required, isolating the desired reaction product.

Process steps (g) and (h) may be carried out in exactly analogous fashion to process steps (b) and (c) above, for example as hereinafter described in examples E below. The starting materials for process step (g) may be obtained entirely analogously to process step (e) or (f) above by:

i) deprotection of the corresponding cyclosporin wherein the residue at the 1-position is 3'-O-acyl-cis-MeBmt- or, a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms, said residue being in 3'-O-protected form; or

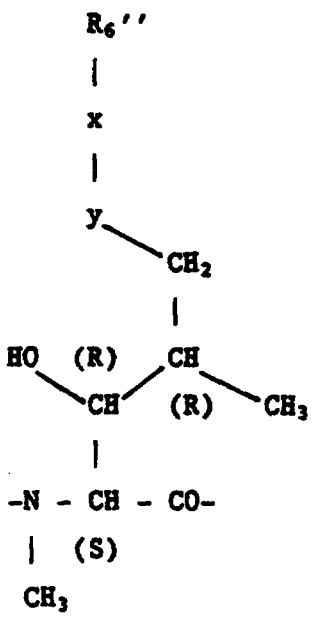
j) reduction of the corresponding cyclosporin wherein the residue at the 1-position is a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue, said residue being in free or 3'-O-protected form and, when required, carrying out process step (i).

Suitable 3'-O-protecting groups are as hereinbefore described in relation to process steps (e) and (f). In carrying out process step (j) unsaturated linkages in the hydrocarbyl moiety will undergo reduction, together with the group -x-y-. Alternatively, cyclosporin starting materials wherein the residue at the 1-position is -cis-MeBmt- may be obtained in accordance with the total synthetic method for the production of cyclosporins, e.g. as described in European patent publication no. 0 034 567 or US patent no. 4 369 542.

The cyclosporin starting materials for process step (g) wherein the residue at the 1-position is other than -cis-MeBmt- are also new and form part of the present invention as novel compounds per se. In a further aspect of the present invention accordingly also provides:

CLASS 6

A cyclosporin wherein the residue at the 1-position is a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms, or a -7-'desmethyl-7'-hydrocarbyl-dihydro-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms and wherein any aliphatic group or moiety as or in said hydrocarbyl moiety is saturated, which residue may be represented by formula XIX'



(XIX')

wherein
-x-y- is cis or trans -CH=CH- or $-CH_2-CH_2-$ and R_6'' is hydrocarbyl having at least two carbon atoms with the proviso that when -x-y- is $-CH_2-CH_2-$ any aliphatic group or moiety present as or in R_6'' is saturated.

Preferred cyclosporins of this class are those of formula II as illustrated above wherein A is a residue of formula XIX' as defined above, B has the meanings given for formula II, X is -Sar- and Y is -Val-.

In addition to their utility as intermediates, cyclosporins of class 6 also possess, e.g. immunosuppressive, anti-inflammatory and anti-parasitic activity as hereinafter described. The said cyclosporins thus have utility in their own right.

Cyclosporins of class 6 also exhibit activity in increasing sensitivity to, or increasing the efficacy of, chemotherapeutic drug therapy and, in particular in reversing chemotherapeutic drug resistance, e.g. antineoplastic or cytostatic chemotherapy, as hereinbefore discussed for cyclosporins of classes 1 to 3. Having regard, e.g. to their inherent immunosuppressive properties, however cyclosporins of class 6 are generally less suitable for use in such indications.

Cyclosporins as herein described and exemplified, wherein the residue at the 1-position is -cis-MeBmt-, while within the purview of the aforementioned European patent publication no. 0 034 567 and U.S. Patent no. 4 369 542, are formally novel.

The following examples are illustrative of the above processes for the preparation of cyclosporins of group $1a^3$ and of class 6.

EXAMPLES E

Preparation of [3'-0-acetyl-7'-desmethyl-7'-phenyl-MeBmt]^1-Ciclosporin (cyclosporin 1.22) and of [3'-0-acetyl-7'-desmethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin (cyclosporin 1.27):

9.5 Benzyltriphenylphosphoniumchloride are dissolved in 150ml dry benzene and reacted with 2.7g potassium-t.butylate for 24 hours under reflux on a water separator. After cooling, the suspension is filtered into a new flask under inert atmosphere. 5g of cyclosporin 5.1 (c.f. examples C) in 50ml benzene are added over a period of 5 minutes. After 21 hours at room temperature, the reaction mixture is poured on ice, the organic phase washed with 2 N HCl, bicarbonate and water dried over sodium sulfate, and evaporated. The residue is chromatographed twice on 440g silica gel (0.04 - 0.063mm) with chloroform containing 8 to 30 p.p.vol. acetone. Fraction 2 contains cyclosporin 1.27 fractions 5 - 15 cyclosporin 1.22. Cyclosporins 1.23 to 1.26 and 1.28 to 1.34 may be prepared analogously. These cyclosporins have the following physical characteristics.

	Physical data:
1.22	$[\alpha]_D^{20}$= -210.9°(c= 1.37 in $CHCl_3$)
1.23	$[\alpha]_D^{20}$= -234.9°(c= 0.89 in $CHCl_3$)
1.24	$[\alpha]_D^{20}$= -248.97°(c= 1.17 in $CHCl_3$)
1.25	$[\alpha]_D^{20}$= -237.3°(c= 0.39 in $CHCl_3$)
1.26	NMR.IR { Ester 1740; Acetate 1230 } in CH_2Cl_2

1.27	$[\alpha]_D^{20}$= -235.8°(c= 1.0 in $CHCl_3$)
1.28	$[\alpha]_D^{20}$= -220°(c= 1.75 in $CHCl_3$)
1.29	$[\alpha]_D^{20}$= -239.07°(c= 0.97 in $CHCl_3$)
1.30	$[\alpha]_D^{20}$= -207.8°(c= 1.25 in $CHCl_3$)
1.31	$[\alpha]_D^{20}$= -239.6°(c= 0.91 in $CHCl_3$)
1.32	NMR.IR { Ester 1746; Acetate 1228; MH^+ 1271 } in CCl_4
1.33	NMR.IR { Ester 1745; Acetate 1225; MH^+ 1271 } in CCl_4
1.34	$[\alpha]_D^{20}$= -226.23°(c= 1.447 in $CHCl_3$)

EXAMPLES F

Preparation of cyclosporins of class 6.

Preparation of [7'-desmethyl-7'-phenyl-MeBmt]^1-Ciclosporin (cyclosporin 6.1)

2.29g of cyclosporin 1.22 obtained as above are dissolved in 20ml methanol : water (4.5 : 1) containing 1.67g potassium carbonate. After 20 hours at room temperature, the reaction mixture is poured on ice containing 10% of tartaric acid and extracted with chloroform. The crude extract is chromatographed on 120g silica gel (0.04 - 0.063mm) with dichloromethane, containing increasing amounts (20-30%) of acetone, to give the title compound: $[\alpha]_D^{20}$ = -209° (c = 0.99 in $CHCl_3$).

The following cyclosporins are obtained analogously:

6.2 [7'-Desmethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -236° (c = 1 in $CHCl_3$);

6.3 [7'-Desmethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -249° (c = 1.17 in $CHCl_3$);

6.4 [7'-Desmethyl-7'-vinyl-cis-MeBmt]^1-[Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -248° (c = 1.44 in $CHCl_3$);

6.5 [7'-Desmethyl-7'-(3-methyl-n.butyl)-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -240° (c = 1.15 in $CHCl_3$);

6.6 [7'-Desmethyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -220° (c = 1.75 in $CHCl_3$);

6.7 [7'-Desmethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -239° (c = 0.97 in $CHCl_3$);

6.8 [7'-Desmethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -208° (c = 1.025 in $CHCl_3$);

6.9 [7'-Desmethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -240° (c = 0.91 in $CHCl_3$);

6.10 [7'-Desmethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -254.8° (c = 0.48 in $CHCl_3$);

6.11 [7'-Desmethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin: $[\alpha]_D^{20}$ = -246.1° (c = 0.52 in $CHCl_3$);

6.12 [7'-Desmethyl-7'-(3-bromo-n.propyl)-cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -226° (c = 1.14 in $CHCl_3$);

De-protection of cyclosporin 1.23 leads to the production of [cis-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -235 (c = 0.9 in $CHCl_3$).

Preparation of [7'-Desmethyl-7'-phenyl-dihydro-MeBmt]^1-Ciclosporin (cyclosporin 6.13)

796mg of a mixture of cyclosporins 6.1 and 6.2 are hydrogenated in 50ml ethanol over 100mg 10% Pd on charcoal at room temperature during 6 hours. Filtration over Hyflo yields the pure title compound: $[\alpha]_D^{20}$ = -210° (c = 0.7 in $CHCl_3$).

The following cyclosporins are obtained analogously:

6.14 [7'-Desmethyl-7'-n.propyl-dihydro-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -188° (c = 6.16 in $CHCl_3$), obtained from cyclosporin 6.6 or 6.7;

6.15 [7'-Desmethyl-7'-ethyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin: $[\alpha]_D^{20}$ = -224° (c = 0.4 in $CHCl_3$), obtained from cyclosporin 6.4;

6.16 [7'-Desmethyl-7'-(3-methyl-n.butyl)-dihydro-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -222° (c = 0.995 in $CHCl_3$), obtained from cyclosporin 6.5;

6.17 [7'-Desmethyl-7'-i.propyl-dihydro-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -229° (c = 1.32 in $CHCl_3$);

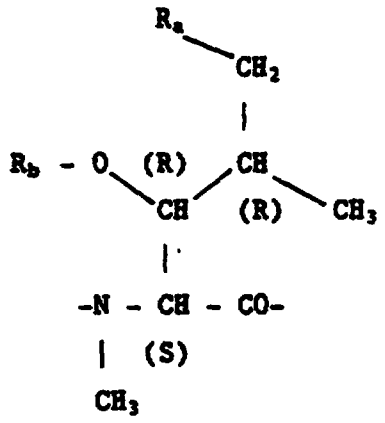
6.18 [7'-Desmethyl-7'-ethyl-dihydro-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -232.9° (c = 0.48 in $CHCl_3$), obtained from cyclosporin 6.10;

6.19 [7'-Desmethyl-7'-ethyl-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin: $[\alpha]_D^{20}$ = -227.29° (c = 0.54 in $CHCl_3$), obtained from cyclosporin 6.11;

6.20 [7'-Desmethyl-7'-phenyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporin: $[\alpha]_D^{20}$ = -214° (c = 1.19 in $CHCl_3$), obtained from cyclosporin 6.8 or 6.9;

6.21 [7'-Desmethyl-7'-ethyl-dihydro-MeBmt]^1-Ciclosporin: $[\alpha]_D^{20}$ = -233° (c = 1.15 in $CHCl_3$), obtained from cyclosporin 6.3;

As will be apparent, cyclosporins of groups $1a^2$ and $1a^3$ and of classes 4, 5 and 6 herein before described, all of which are novel, are structurally related and may, for convenience, readily be subsumed into unified categories, e.g. comprising cyclosporins wherein the residue at the 1-position is a residue of formula XXI



(XXI)

wherein

(i) R_a is formyl and

R_b has the meanings given for R_{12} in relation to formula XVIII; or

(ii) R_a is -x'-y'-R_c whereby -x'-y'-R_c has the meanings given for -x-y-R_4, -x-y-R_5 or -x-y-R_5'' in relation to formulae IV, V, XIV and XIX' above and

R_b is hydrogen or acyl.

Similarly cyclosporins of groups $1a^2$ and $1a^3$ and of classes 4 and 6, all of which are novel and have utility other than as intermediates can be subsumed into unified sub-categories, e.g. comprising cyclosporins wherein the residue at the 1-position is a residue of formula XXI as illustrated above, wherein R_a and R_b have the meanings given under (ii) for the formula XXI.

Acyl groups as R_b are preferably groups $ACYL^1$ as defined in relation to formulae III and IV, in particular (C_{1-4} alkyl)-carbonyl, e.g. acetyl.

Preferred cyclosporins of such categories/sub-categories are those of formula II as illustrated above wherein A is a residue of formula XXI as defined above and B has the meanings given for formula II, X is -Sar- and Y is -Val-.

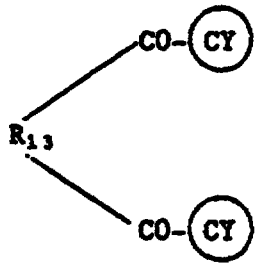
Various cyclosporins of group 1b) as hereinbefore set forth, e.g. wherein the residue at the 2-position is a residue of formula III' as illustrated above in which $ACYL^3$ is acetyl are known. Thus cyclosporin 1.35 is known and has been described, together with processes for its production in Traber et al., Helv. Chim. Acta, 60, 1247 at seq./(1977). Other cyclosporins of group 1b may be prepared analogously. Cyclosporin 1.36 however is of an entirely novel type. A still further group of cyclosporin in accordance with the present invention accordingly comprises.

Group 1e)

i) A dicarboxylic acid di-ester of a cyclosporin having a β-hydroxy-(L)-α-amino acid residue at the 2-position; in particular:

ii) A dicarboxylic acid di-ester of cyclosporin having an (L)-threonyl residue at the 2-position; and especially

iii) A dicarboxylic acid di-ester of formula XXII

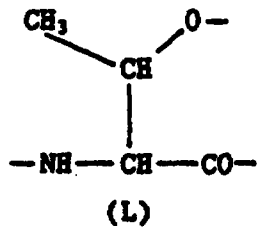


(XXII)

wherein R_{13} is C_{1-8} alkylene and each



represents a residue of formula II as illustrated above wherein
A is -MeBmt- or -dihydro-MeBmt-
B is an (L) threonyl residue of formula XXIII



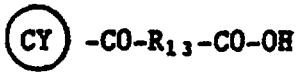
(XXIII)

X is -Sar- and Y is -Val-.

Preferably R_{13} is C_{1-4} alkylene.

The present invention also provides a process for the preparation of a cyclosporin of group 1e which process comprises

k) reacting a β-O-hemiester of cyclosporin wherein the residue at the 2-position is a β-hydroxy-(L)-α-amino acid residue, for example a β-O-hemiester of formula XXIV



(XXIV)

wherein



and R_{13} have the meanings given above, or a reactive functional derivative thereof, with a cyclosporin wherein the residue at the 2-position is a β-hydroxy-(L)-α-amino acid residue, for example a cyclosporin of formula II as illustrated above, wherein A is -MeBmt- or -dihydro-MeBmt-, B is -Thr-, X is -Sar- and Y is -Val-.

Reaction may suitably be effected in accordance with the general procedures of the following example G.

EXAMPLE G

Preparation of 1,2-ethanedicarboxylic acid [O-(L) threonyl]^2-Ciclosporin di-ester (cyclosporin 1.36)

0.255g 2-chloro-1-methyl-pyridinium iodide and 0.244g 4-dimethylamino pyridine are added to 1.318 g [(O-hemisuccinyl)-Thr]^2-Ciclosporin in 5ml absolute CH_2Cl_2 at 0 °C. 1.218g [Thr]^2-Ciclosporin are added, the reaction mixture stirred for 3 hrs. at 0 °C, and the temperature allowed to rise to 20 °C with further stirring. The reaction mixture is diluted with CH_2Cl_2 and shaken with 10ml 0.1 NaOH with added ice. The mixture is washed 2x with H_2O and the organic phase dried over Na_2SO_4 filtered and evaporated. The raw product is purified chromatographically employing silica gel and hexane/acetone (1:1) as eluant to yield the title compound: $[\alpha]_D^{20}$: -209.4 ° (c = 0.5 in $CHCl_3$).

The [(O-hemisuccinyl)Thr]^2-Ciclosporin required as starting material is known - see e.g. International Patent Application No. PCT/EP85/00501, International Patent Application No. WO86/02080, example 5. Other hemiester starting materials suitable for the preparation of cyclosporins of group 1e may be prepared analogously.

Cyclosporins of group 1c as hereinbefore set forth are new and form part of the present invention as novel compounds per se.

The present invention also provices a process for the production of cyclosporins of group 1c, which process comprises.

1) oxidising a cyclosporin wherein in the residue at the 1-position is 3'-hydroxy substituted for example is -MeBmt-.

Step 1) above may be performed e.g. by reaction with N-chloro-succinimide/dimethylsulfide at a temperature of e.g. -30° to 10°C, e.g. in accordance with the procedures of example H below.

EXAMPLE H

Preparation of [3'-desoxy-3'-oxo-MeBmt]^1-Cyclosporin (Cyclosporin 1.37)

8.48ml dimethylsulfide are added at 0°C to a solution of 12.8g N-chlorosuccinimide in 400ml toluene. The mixture is stirred for 5 mins. at 0°C, cooled to -12°C and 9.62g Ciclosporin in 40 ml toluene are added. The obtained suspension is stirred for 1.5 hrs. at -10°C and for 1.0 hrs. at -10 to -5°C. 19.4g triethylamine are added, whereupon a light precipitate forms. The mixture is stirred for 5 hrs. at 0°C, and diluted with 250ml ethyl ether. 192ml 1N HCl are added cold and extracted. The organic phase is washed 2x with 500ml H_2O, shaken with 250ml 10% cold $NaHCO_3$ and washed 2x with 500 ml H_2O, 250 ml 10% tartaric acid and again with H_2O. The acid and basic aqueous solutions are re-extracted with 2 x 500ml ethyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness at 40°C. The residue is purified chromatographically employing 300g silica gel and saturated aqueous ethyl acetate to yield the title compound: $[\alpha]_D^{20}$ = -241.3° (c = 0.531 in $CHCl_3$) and -169.5° (c = 0.5 in CH_3OH).

Cyclosporins 1.38 and 1.39 may be prepared analogously:

	Physical data:
1.38	$[\alpha]_D^{20}$= -255.1°(c= 0.5 in $CHCl_3$)
1.39	$[\alpha]_D^{20}$= -235.4°(c= 0.5 in $CHCl_3$)

Cyclosporins of group 1d as hereinbefore set forth are also new and also form part of the present invention as novel compounds per se.

The present invention also provides a process for the production of cyclosporins of group 1d, which process comprises:

m) oxidising, e.g. selectively oxidising, a cyclosporin wherein the residue at the 2-position is a β-hydroxy-α-amino acid residue, for example an (L)-threonyl residue.

Process step (m) may be carried out entirely analogously to process step (1) above, e.g. in accordance with the general procedures of the following example I.

EXAMPLE I

Preparation of [α-Methylketo-Gly]^2-Ciclosporin (Cyclosporin 1.40)

484mg dimethylsulfide are added to 868mg N-chlorosuccinimide in 26ml toluene at 0°C. After stirring for 10 mins. at 0°C the suspension is cooled to -30°C and 1584mg [Thr]^2-ciclosporin in 6.5ml toluene are added. The reaction mixture is stirred for 1 hr. at 26 - 30°C and 1.81ml triethylamine are added. Cooling is removed and after a further 5 mins. 25ml ethyl ether are added. The reaction mixture is poured onto 150ml ice water / 10ml 1N HCl and stirred and a further 100ml ethyl ether are added. The organic phase is washed 3x with 150ml ice water and extracted 2x with ethyl ether. The combined organic phases are dried over Na_2SO_4 and concentrated. The residue is dissolved in 10ml CH_2Cl_2, filtered throught Hyflo, diluted with hexane and evaporated to yield the title compound: $[\alpha]_D^{20}$ = -229° (c = 1.0 in $CHCl_3$) and -184.8° (c

= 1.0 in CH_3OH).

Cyclosporin 1.41 may be prepared analogously:

$[\alpha]_D^{20}$ = -226.7° (c = 1.0 in $CHCl_3$).

Cyclosporins of class 2(i) and of class 2(ii) as hereinbefore set forth are also new and form part of the present invention as novel compounds per se.

In addition the present invention also provides a process for the production of cyclosporins of class 2(i) and 2(ii), which process comprises:

m) for the production of a cyclosporin of class 2(i), reacting a cyclosporin wherein the 3'-carbon atom of the residue at the 1-position is oxo-substituted, e.g. a cyclosporin wherein the residue at the 1-position is -3'-desoxy-3'-oxo-MeBmt- with a C_{1-4}alkoxyamine, or

n) for the production of a cyclosporin of class 2 (ii), cyclising an open-chain peptide comprising the sequence of a cyclosporin comprising an (L)-isoleucyl residue at the 2-position, said open-chain peptide commencing with the residue corresponding to residue 8 of said cyclosporin as N-terminal and terminating with the residue corresponding to residue 7 of said cyclosporin as C-terminal, for example cyclising an open-chain peptide comprising the sequence

-(D)Ala-MeLeu-MeLeu-MeVal-MeBmt-Ile-Sar-MeLeu-Val-MeLeu-Ala-

8 9 10 11 1 2 3 4 5 6 7

Step (m) above may be performed, e.g. by reaction with the chosen C_{1-4}alkoxyamine, suitably in acid addition salt form, in the presence of a base, such as pyridine, at temperatures of from about -10° to about 80°C, for example in accordance with the general procedures of example J below.

Process step (n) above may be carried out entirely analogously to the general procedures for the total synthesis of cyclosporins, e.g. as described in U.S. patent no 4 554 531 or European patent publication no. 0 098 456. Thus cyclosporin 2.2 is prepared e.g. by substitution of BOC-Ile-OH for BOC-αAbu-OH at step a) of example 1 of said patent/patent publication, and proceeding subsequently in directly analogous fashion to steps (b) through (x) as described in said patent/patent publication.

Cyclosporin 2.2 itself has the following characterising data:

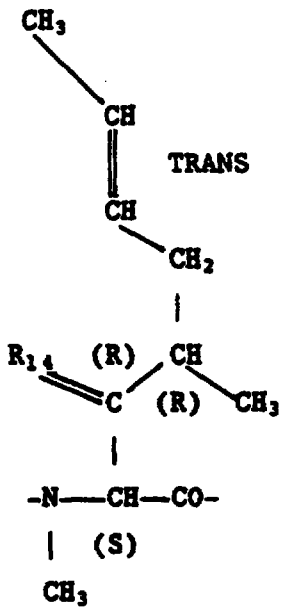
M.P. = 151°C / $[\alpha]_D^{20}$ = -224° (c = 1.0 in $CHCl_3$)

EXAMPLE J

Preparation of [3'-Desoxy-3'-methoxyimino-MeBmt]^1-Ciclosporin (Cyclosporin 2.1)

600mg of the product of example H and 835mg methoxylamine hydrochloride in 2.5ml ethanol/2.5ml pyridine are stirred for 14 hrs. at 50°C under an atmosphere of argon. The pyridine is evaporated off and the remainder filtered. The filtrate is taken up in CH_2Cl_2 and washed with brine. The brine is extracted several times with CH_2Cl_2 and the combined organic phases again washed with brine, dried and evaporated. The residue is purified chromatographically to yield the title compound: $[\alpha]_D^{20}$ = -214° (c = 1.09 in $CHCl_3$).

As will be apparent cyclosporins of group 1c and of class 2(i) hereinbefore described, all of which are novel and have utility other than as intermediates can be subsumed into unified sub-categories, e.g. comprising cyclosporins wherein the residue at the 1-position is a residue of formula XXV



(XXV)

wherein R_4 is oxygen or a group of formula $R_{15}N=$ wherein R_{15} is C_{1-4} alkoxy.

Cyclosporins of class 2(iii) are known. Thus cyclosporins 2.3 to 2.6 are described e.g. in Wenger, Transplantation Proc., XVIII (6) Supp. 5 (December), 213 et seq. (1986). These cyclosporins, as well as other cyclosporins of class 2(iii) may be prepared in accordance with the general procedures for the total synthesis of cyclosporins, e.g. as described in U.S. patent no. 4 554 531 and European patent publication no. 0 098 456, e.g. by substitution of H-MeIle-Bzl of H-MeAlolle-Bzl for H-MeVal-Bzl at step (g) of example 1 thereof. Cyclosporins 2.3 to 2.5 have the following characterising data:

CYCLOSPORIN	m.p. (°C)	$[\alpha]_D^{20}$ = -; (c = - in $CHCl_3$)
2.3	162 - 163	- 178°; 1.0
2.4	144 - 146	- 221°; 1.0
2.5	146 - 146	- 225°; 1.0
2.6	148	- 170°; 1.0

Cyclosporins 3.1 to 3.5, 3.7 and 3.9 of class 3 are known [see e.g. Traber et al., Helv. Chim. Acta, 65, 1655 et seq. (1982) and 70, 13 et seq. (1987)].

Cyclosporins 3.6, 3.8 and 3.10 are new and are part of the present invention as novel compounds per se.. 3.6 and 3.8 may be prepared in a manner entierly analogous to that used for the preparation of other, known dihydrocyclosporins e.g. as hereinbefore described in relation to process step (f).

Cyclosporin 3.10 may be prepared in accordance with general procedures for the separation of cyclosporin minor metabolites., e.g. as described in Helv. Chim. Acta 65, 1655 et seq. (1982), as a minor metabolite fraction from fermentation broths used in the production of [(D)Ser]^8-Ciclosporin (see European patent publication no. 0 056 782), e.g. as described in the following example K.

EXAMPLE K

Preparation of [MeLeu]^1-Ciclosporin (cyclosporin 3.10)

The biomass obtained following cultivation in accordance with example 3 of European patent publication no. 0 056 782 is spun-down in a clarifying separator (Westfalia) and the liquid phase (culture filtrate) extracted 3x, each time with the equivalent amount of ethyl acetate. The ethyl acetate extracts are concentrated under vacuum. The solid phase (mycelium) is treated with methanol and homogenised and solid and liquid phases separated in a clarifying separator. This extraction procedure is repeated 2x using 90% methanol. The methanolic extracts are combined, water is added and the extracts concentrated under vacuum. The remaining aqueous extract concentrate is extracted 3x with the equivalent amount of ethyl acetate and the ethyl acetate extracts concentrated under vaccum. Both raw-extracts (from the culture filtrate and the mycelium) are chromatographed using silica gel (0.040-0.063 mm) and H_2O-saturated ethyl acetate. Early eluting fractions contain primarily [Val]^2-Ciclosporin (cyclosporin D) followed by fractions containing primarily [MeLeu]^1-Ciclosporin (cyclosporin 3.10) and Ciclosporin (cyclosporin A). Peak fractions are chromatographed again using silica gel (0.020-0.045 mm) and acetone/hexane (1:1) as eluant. [MeLeu]^1-Ciclosporin containing fractions are re-chromatographed using LiChoprep® RP-18 (0.040-0.063 mm) and methanol/H_2O (85:15) as eluant and then silica gel (0.020-0.045 mm) and H_2O-saturated ethyl acetate as eluant, to yield the title compound: m.p. = 142-148 °C, $[\alpha]_D^{20}$ = -303° (c = 0.54 in $CHCl_3$).

Physical characteristics for cyclosporin 3.6 are:

m.p. = 180-182 °C; $[\alpha]_D^{20}$ = -211° (c = 0.64 in $CHCl_3$).

As already indicated it has, in accordance with the present invention, now been found that cyclosporins of clases 1 (including cyclosporins of groups 1a^1 to 1a^5 and 1b to 1e, 2 and 3 and, in particular, individual cyclosporins of these classes hereinbefore specifically named, are capable of increasing or enhancing effectiveness of, or increasing or enhancing sensitivity to, other chemotherapeutic drug therapy, in particular anti-microbial (e.g. anti-bacterial, anti-viral, antifungal or anti-protozoal) chemotherapy and, especially anti-cancer or anti-tumor (e.g. anti-neoplastic or cytostatic) chemotherapy. They are accordingly indicated for use, e.g. as a means of reducing regular chemotherapeutic dosage levels, for example, in the case of anti-neoplastic or cytostatic drug therapy, as a means of decreasing overall drug toxicity and, more especially, as a means of reversing or reducing resistance, including both inherent and acquired resistance, to chemotherapy.

EXAMPLE 1

Utility in restoring sensitivity to anti-neoplastic/cytotoxic, anti-tumor drug substances (in vitro - 1)

Cancer cell lines (CCL), e.g. from human small cell carcinoma of the lung, resistant to one or more cancer therapeutic drug substances (CTDS) selected from the group comprising Daunorubicin (DR); Vincristine (VC); Adriamycin (AM); Etoposide (ET); Tenoposide (TE); and Colchicine (CC) are developed in accordance with the methods described by Twentyman et al., Br. J. Cancer, 54, 253 (1986).

Sensitivity of resistant sub-lines (CCL-R) is compared with parental sensitive lines (CCL-S) by assaying inhibition of cell growth during continuous CTDS exposure, e.g. in the case of a DR-resistant line (CCL-DRR) by comparing growth of CCL-DRS and CCL-DRR lines in the presence of DR contained in the growth medium ab-initio. For the purpose, cell proliferation is measured by cell counting using an electronic cell counter, counting being effected close to termination of the exponential growth phase. CCL-R lines are selected for which the IC_{80} (drug concentration e.g. DR concentration, required to reduce final cell number to 20% of that for non-CTDS (e.g. DR) treated controls is >80 X, preferably >100 X, greater than that of parental CCL-S lines.

Sensitivity of selected CCL-R lines to CTDS (e.g.DR) in the presence and absence of test cyclosporin is then performed, employing cell count as a measure of proliferation as described above. For this purpose cells are cultured ab initio in the presence of varying concentrations of both CTDS and test cyclosporin. For screening, concentrations of the latter are chosen which do not themselves cause a significant reduction in proliferation. Appropriate concentrations are established by culturing CCL-S and CCL-R in the presence of varying concentrations of cyclosporin in the absence of CTDS. Cyclosporins are routinely tested at concentrations of from 0.01 to 50, in particular 0.1 to 10, µg/ml, e.g. at concentrations of 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10.0 and 50 µg/ml. The ratio of CTDS (e.g. DR) required to inhibit cell proliferation by 50% in the absence of test cyclosporin (IC_{50}-CS) compared with that obtained in the presence of test cyclosporin (IC_{50} + CS) is taken as a measure of increased sensitivity of the CCL-R line to

CTDS which has been induced by the cyclosporin. Stability of the CCL-R line used is ensured by cross checking its sensitivity to CTDS with that previously established.

In the above test model, cyclosporins of classes 1 to 3, in particular specific cyclosporins recited, are effective in increasing sensitivity to CTDS (e.g. DR, VC, AM etc.) at the above indicated concentrations in particular at concentrations of ca. 10 µg/ml, or less.

At higher concentrations, e.g. ca. 50 µg/ml inhibition of proliferation of both CCL-S and CCL-R lines is, in particular instances, occasioned by test cyclosporins in the absence of CTDS, though where this occurs the phenomenon is generally less marked in CCL-R than CCL-S lines. More significantly, test cyclosporins are found to be effective in increasing sensitivity to CTDS in CCL-R lines at concentrations which have no influence on cell proliferation in the absence of CTDS.

Thus in one series of trials employing an AM resistant human small lung cancer cell line, and cyclosporins 2.4, 1.1 and 1.35, established AM sensitisation ratios (AM IC_{50} - CS / AM IC_{50} + CS) are as follows*:

	SENSITISATION RATIO	
	CYCLOSPORIN CONCENTRATION	
CYCLOSPORIN	50.0 µg/ml	5.0 µg/ml
2.4	>30	>30
1.1	---	>20
1.35	12	3.3
NONE	1.0	1.0

[*Investigation and data from P.R. Twentyman, MRC Clinical Oncology and Radiotherapeutic Unit, Hills road, Cambridge, England - c.f. Br. J. Cancer, 57, 254-258 (1988)]:

EXAMPLE 2

Utility in restoring sensitivity to anti-neoplastic/cytotoxic, anti-tumor drug substances (in vitro - 2).

Testing may be performed employing any appropriate drug resistant cell line and control (parental) cell lines, generated, e.g. as described by Ling et al., J. Cell. Physiol. 83, 103-116 (1974) and Bech-Hansen et al. J. Cell. Physiol. 88, 23-32 (1976). Particular clones chosen are the mutli-drug resistant (e.g. colchicine resistant) line CHR (subclone C5S3.2) and the parental, sensitive line AUX B1 (subclone AB1 S11) - c.f. Ling et al. loc. cit. and Juliano et al. Biochim. Biophys. Acta, 455, 152-162 (1976); Carlsen et al. Biochim. Biophys. Acta. 455, 900-912 (1976); Lalande et al., Proc. Natl. Acad. Sci., 78 (1), 363-367 (1981); Kartner et al., Science 221, 1285-1288 (1983); Kartner et al., Nature, 316, 820-823 (1985); Riordan et al., Nature, 316, 817-819 (1985); Van der Blick et al., Mol. Cell. Biol. 6, 1671-1678 (1968); Endicolt et al., Mol. Cell Biol., 7, 4075-4081 (1987); Deuchars et al., Mol. Cell. Biol., 7, 718-724 (1987); and Gerlach et al., Nature, 324, 485-489 (1986).

Cell lines are grown in αMEM medium supplemented with (L)-asparagine 0.02mg/ml, MEM vitamins (IX), penicillin-streptomycin 100 UT/ml, (L)-glutamine 2mM and 10% heat-inactivated fetal calf serum. Assay is performed using 96 well plates. 50µl colchicine solution are added in the culture medium in triplicates to obtain final concentrations of 30-10-3-1-0.3-0.1-0 µg/ml for the resistant line (RL) and of 0.3-0.1-0.03-0.01-0.003-0.001-0 µg/ml for the sensitive line (SL). Further down-extension of the dose range is performed as necessary, i.e. when test cyclosporin very greatly decreases the IC_{50} response to colchicine.

Test cyclosporins are dissolved at 1mg/ml in abs. C_2H_5OH. Each test cyclosporin is screened routinely at 0.1 and 1.0 µg/ml, with controls being treated with the corresponding C_2H_5OH solvent dilutions. Test cyclosporin or control are added (50µl) to each well and mixed with colchicine solutions already present. 100µl cellular suspensions at $4x10^3$ cells/ml for SL (400 cells/well) and $8x10^3$ cells/ml for RL are added.

Proliferation is measured by colorimetric assay [Mosman, J. Immunol. Methods, 65, 55-63 (1983)] using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT). First 100µl cell-free supernatant is

removed, then 10µl MTT solution at 5mg/ml in RPMI 1640 medium (Gibco) are added to each plate and the plate incubated for 3 hrs. at 37°C. 100µl butanol/isopropanol/1N HCl (192:96:12 ml) are then added to each plate and the plates shaken until complete dissolution. Optical density (OD) is read at 540 nm.

Extend of cell growth (measured by MTT-dependent OD) is represented as a function of colchicine concentration, a dose-response curve being constructed for each test cyclosporin, and the colchicine IC_{50} - (CIC_{50}) (i.e. the concentration of colchicine required to reduce proliferation by 50%) determined.

Increase of colchicine sensitivity induced by each test cyclosporin at both 0.1 and 1.0µg/ml is determined as:

$$\frac{CIC_{50} \text{ in absence of test cyclosporin}}{CIC_{50} \text{ in presence of test cyclosporin}} = \frac{CIC_{50}-}{CIC_{50}+} = \text{gain in sensitivity}$$

Test cyclosporins may influence colchicine sensitivity in both RL and SL. Relative influence in the two lines may be determined as:

$$\frac{CIC_{50}+ \text{ for RL lines}}{CIC_{50}+ \text{ for SL lines}} = \frac{CIC_{50} + RL}{CIC_{50} + SL} = \text{relative resistance}$$

Cyclosporins of classes 1 to 3 increase sensitivity of RL to colchicine at concentrations indicated above. Increase of sensitivity of SL is commonly observed at equivalent concentrations though is generally less than for RL. For use in accordance with the present invention, cyclosporins exhibiting higher relative resistance as defined above are generally considered more suitable. In one series of experiments the following gains in sensitivity to colchicine as defined above were, for example recorded for RL and SL.

CYCLOSPORIN	SL		RL	
	0.1µg/ml	1.0µg/ml	0.1µg/ml	1.0µg/ml
1.1	4.0	8.0	1.4	30.8
1.2	4.4	8.1	2.0	59.8
1.3	5.3	10.7	1.8	97.9
1.4	6.7	11.7	1.7	97.6
1.10	3.6	11.6	1.1	28.9
1.11	6.3	17.6	1.1	36.7
1.15	4.7	12.9	1.5	38.3
1.37	5.8	12.1	1.4	82.4
2.2	7.9	15.1	1.5	97.3
2.4	4.7	15.7	1.2	34.5

EXAMPLE 3

Utility in restoring sensitivity to anti-neoplastic/cytotoxic, anti-tumor drug substances (in vivo)

Ehrlich ascites carcinoma (EA) sub-lines resistant to drug substance DR, VC, AM, ET, TE or CC are developed by sequential transfer of EA cells to subsequent generations of BALB/c host mice in accordance with the methods described by Slater et al., J. Clin. Invest, 70, 1131 (1982). For this purpose drug substance is administered at a dosage of 0.2 to 0.5 mg/kg, i.p. daily over 5 doses, starting 24 hours after inoculation of host mice with 0.2 ml undiluted malignant ascites harvested from pre-terminal animals.

For the test proper, host mice receive resistant EA-R or sensitive (parent) EA-S, EA lines as described above. Mice receiving EA-R are divided into groups receiving:

1. No drug / No cyclosporin
2. Drug-substance therapy / No cyclosporin
3. No drug / Test cyclosporin
4. Drug-substance + Test cyclosporin.

Anti-neoplastic drug substance is administered at dosages employed in generating EA-R lines. Cyclosporin test substance is administered at a total test dosage in the range of from 1 to 80 mg/kg, in particular 5 or 25 or up to 40 mg/kg in 5 divided daily doses, i.p. (in ethanol/olive oil) starting 24 hours after inoculation with EA-R. Mean-survival time in groups 2, 3 and 4 are compared with group 1 as measure of efficacy of applied therapy.

Results obtained show no significant difference in mean-survival time between groups 1, 2 and 3. In group 4, receiving cyclosporin of classes 1 to 3 at dosages as indicated above, substantial increase in survival time (e.g. of the order of 2 to 3 fold or greater) as compared with both groups 1 and 2 is observed.

Equivalent results may be obtained employing cyclosporins of classes 1 to 3 in test models of comparable design, e.g. in vitro, or employing test animals infected with drug-resistant viral strains, antibiotic (e.g. penicillin) resistant bacterial strains, anti-mycotic resistant fungal strains as well as drug resistant protozoal strains, e.g. Plasmodial strains, for example naturally occurring sub-strains of Plasmodium falciparum exhibiting accquired chemotherapeutic, anti-malarial drug resistance.

Utility of cyclosporins of classes 1 to 3 in accordance with the present invention can also be demonstrated in clinical trials, for example preliminary trials, performed as follows:

CLINICAL TRIAL 1

Subjects (♂ and ♀) are selected from patients diagnosed as exhibiting malignant cancerous growth and to be submitted to anti-neoplastic / cytostatic drug therapy. A detailed report is submitted for each subject entered in the trial detailing case history, disease status, estimated rate of disease progression and estimated prognosis.

Type of anti-neoplastic / cytostatic drug therapy to be applied and estimated dosage rate required in the absence of cyclosporin therapy is determined by the attending physician, having regard to the type and extent of the cancer.

Trial cyclosporin is administered orally at a dosage rate of from 1.0 to 20.0 mg/kg/day or parenterally, e.g. i.v. or i.m., a a dosage rate of from 0.5 to 5.0 mg/kg/day. Where disease status permits, treatment with trial cyclosporin commences at least 1 or 2 days, preferably 10 to 14 days before initiating anti-neoplastic therapy in order to permit build-up to on-going therapeutic dosage levels. In such instances initiating cyclosporin dosages are at the lower end of the above indicated dosage ranges (e.g.: p.o., of the order of from 1.0 to 5.0 mg/kg/day; or parenterally, or the order of from 0.5 to 1.5 mg/kg/day) rising to higher dosage level (e.g. p.o., of the order of from 5.0 to 15.0 or up to 20.0 mg/kg/day or, parenterally, of the order of from 2.0 to 5.0 mg/kg/day), precise regimen being determined by the attending physician having regard to the subject's condition at trial entry. In some cases, it may be required that cyclosporin and anti-neoplastic / cytostatic therapy be initiated and terminated concomitantly, though again with preference for lower initiating cyclosporin dosaging, rising daily to the indicated maximum.

Initiating anti-neoplastic / cytostatic therapy is commenced at ca. 1/3 the estimated dosage rate required in the absence of cyclosporin therapy, precise choice of initiating dosage again being at the discretion of the attending physician. Anti-neoplastic / cytostatic dosaging is increased as required by observed response.

All relevant clinical parameters are monitored throughout the course of the trial, including cyclosporin and anti-neoplastic / cytostatic drug administration rates. Subjects are monitored for control / reduction in tumor growth / occurrence of metastases and possible tumor regression. Reports on disease status and estimated prognosis are submitted at intervals during the course of the trial.

Evaluation of trial results indicate that subjects entered exhibit effective control of or improvement of condition, with restriction of tumor growth or tumor regression and reduction of metastases at anti-neoplastic / cytostatic drug dosage rates below those estimated to be required for equivalent efficacy in the absence of cyclosporin therapy. Reduced incidence of anti-neoplastic / cytostatic drug resistance as compared with reports for groups receiving anti-neoplastic / cytostatic therapy only is recorded, as well as reduced incidence of adverse toxic reaction to administered anti-neoplastic / cytostatic therapy.

CLINICAL TRIAL II

Subjects are chosen from hospitalised or out-patient subjects (♂ and ♀) exhibiting late phase, malignant cancerous growth of whatever type. Subjects selected for trial are patients who have run a full course of anti-neoplastic/cytostatic drug therapy, and who are generally at a late phase of multiple drug treatment and exhibiting renewed onset of tumor growth/metastases etc., i.e. whose cancer is prima facie identifiable as multiple-drug resistant.

A detailed report is submitted for each subject entered in the trial detailing in particular drug therapy applied in the course of the previous 6 to 18 months to date, previous history and current disease status, e.g. estimated rate of disease progression and estimated prognosis.

For the purposes of the trial, entered subjects are maintained on predetermined dose and schedule of anti-neoplastic/cytostatic drug therapy, therapy chosen being that applied at identification of drug resistance and entry into the trial. Anti-neoplastic drug therapy is maintained throughout the trial at the preresistance-determination levels and schedule. The chemotherapy regimen is supplemented by administration of trial cyclosporin, in oral dosage form at a daily dosage rate of from ca. 1 to ca. 20, e.g. ca. 5 to ca. 15, mg/kg/day or administered parenterally, e.g. i.v., at a daily dosage rate of from ca. 0.5 to ca. 7.5, e.g. from ca. 2.0 to ca. 5.0, mg/kg/day. In some patients cyclosporin therapy may commence 1 to up to 14 days before initiating anti-neoplastic therapy and is continued during the entire treatment period. In other cases, it may be required that cyclosporin and anti-neoplastic therapy be initiated and terminated concomitantly.

Subjects are monitored for reduction in tumor growth/occurrence of metastases and possible tumor regression. Reports on disease status and estimated prognosis at the time of examination are submitted at intervals during the course of the trial. In the event that no improvement in condition or restriction of deterioration is reported within an appropriate period, basic anti-neoplastic/cytostatic drug therapy is varied at the discretion of the responsible clinician to alternative, previously applied therapy. All relevant clinical parameters are monitored throughout the course of the trial, including in particular anti-neoplastic/cytostatic drug and cyclosporin serum levels as well as clearance rates.

Evaluation of trial reports indicated that subjects entered exhibit marked improvement in condition, with restriction of tumor growth or tumor regression and decrease in metastases following introduction of cyclosporin therapy, with on-going improvement in disease prognosis.

Cyclosporins of classes 1 to 3 are accordingly indicated for use in the treatment of morbid conditions exhibiting acquired resistance to chemotherapeutic drug treatment, or as adjuvants to chemotherapeutic drug treatment.

The present invention accordingly provides:

1.1 A method of improving or increasing the efficacy of, or of increasing sensitivity to, chemotherapeutic drug therapy; or

1.2 A method of reducing effective chemotherapeutic drug dosage rate;

in a subject in need thereof which method comprises co-administration of a cyclosporin of classes 1 to 3 as hereinbefore defined; or

2.1 A method of treating morbid conditions exhibiting or characterised by resistance, whether accquired, induced or inate, to chemotherapeutic treatment; or

2.2 A method of enhancing or improving chemotherapeutic treatment of morbid conditions exhibiting or characterised by resistance, whether accquired, induced or inate, to said treatment; or

2.3 A method of reversing or reducing resistance, whether accquired, induced or inate, to chemotherapeutic treatment; or

2.4 A method of restoring sensitivity to chemotherapeutic treatment;

in a subject in need thereof, which method comprises administering to said subject an effective amount of cyclosporin of any one of classes 1 to 3 as hereinbefore defined.

Alternatively the present invention provides:

3. A method of chemotherapeutic treatment in a subject in need thereof which comprises administering an appropriate chemotherapeutically active drug substance together with a cyclosporin of any one of classes 1 to 3 as hereinbefore defined as adjuvant treatment to said drug substance.

The present invention also provides:

4. A cyclosporin of any one of classes 1 to 3 as hereinbefore defined for use in a method as defined under any one of 1.1, 1.2, 2.1, 2.2, 2.3, 2.4 or 3 above; or

5. A cyclosporin of any one of classes 1 to 3 as hereinbefore defined for use in the preparation of a pharmaceutical composition for use in a method as defined under any one of 1.1, 1.2, 2.1, 2.2, 2.3, 2.4 or 3 above.

In that none of the cyclosporins of classes 1 to 3 has previously been proposed or recommended for pharmaceutical or therapeutic use, and in that particular cyclosporins of classes 1 to 3 are indeed novel compounds or cyclosporins of entirely novel type, the present invention also provides:

6. Cyclosporins of classes 1 to 3 as hereinbefore specified, e.g. including individual cyclosporins herein before indicated to be novel as well as cyclosporins of groups $1a^2$, $1a^3$, $1a^4$, $1a^5$, 1d, 1e and of class 2(i) and 2(iii), for use as pharmaceuticals.

Particular conditions/forms of chemotherapeutic treatment to which the methods of the present invention apply include conditions caused by microbial, e.g. viral, bacterial, fungal or protozoal infection, involving strains resistant to one or more anti-microbial or anti-biotic drug substances, e.g. anti-viral, anti-bacterial, anti-fungal or anti-protozoal drug substances.

The methods of the present invention are in particular applicable to the treatment of cancers, e.g. of carcinomas, sarcomas or other tumors or malignant growths, exhibiting induced or accquired resistance to one or more anti-cancer chemotherapeutic drug substances, e.g. anti-neoplastic or cytostatic agents, e.g. anthracyclines or vinca alkaloid drug substances or the specific drug substances daunorubicin, vincristine, adriamycin, etoposide, tenoposide and/or Colchicin, e.g. as a means of reducing or reversing tumor growth, occurrence of metastases etc..

Preferred cyclosporins for use in accordance with the present invention are those exhibiting relatively low immunosuppressive activity, e.g. having substantially no immunosuppressive activity at intended dosage levels or which exhibit immunosuppressive activity of an order which is substantially less, e.g. <50%, of that of Ciclosporin. Particular cyclosporins suitable for use in accordance with the methods of the present invention are cyclosporins hereinbefore specifically defined or recited under classes 1 to 3.

Dosages of cyclosporin to be employed in practicing the above methods will of course vary, e.g. depending on the condition to be treated (for example the disease type and the nature of resistance), the particular cyclosporin to be used, the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration orally at dosages of the order from 1 to 20 or up to 50 mg/kg/day, e.g. of the order of from 5 to 10 or up to 15 mg/kg/day administered once or, in divided doses 2 to 4x per day, or on administration parenterally, e.g. intravenously, for example by i.v. drip or infusion, at dosages of the order from 0.5 to 7.5 up to 10mg/kg/day, e.g. of the order of from 1.5 or 2.0 up to 5.0mg/kg/day.

Suitable daily dosages for patients are thus of order of from 50 to 1,000 up to 2,500mg p.o., e.g. of the order of from 250 to 500/600mg p.o., or of the order of from 25.0 to 375.0 up to 500mg i.v., e.g. of the order of from 75.0 to 100/250mg i.v..

Alternatively and even preferably, dosaging may be arranged in patient specific manner to provide pre-determined trough blood levels, e.g. as determined by RIA technique. Thus patient dosaging may be adjusted so as to achieve regular on-going trough blood levels as measured by RIA of the order of from 50 or 150 up to 500 or 1000ng/ml, i.e. analogously to methods of dosaging currently employed for regular Ciclosporin immunosuppressive therapy.

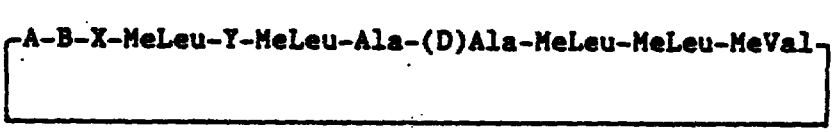
Pharmaceutical compositions suitable for oral administration of cyclosporins of classes 1 to 3 above when practicing the method of the present invention may, for example, be prepared as follows:

INGREDIENT		RELATIVE AMOUNT (g)
i)	Labrafil M 1944 CS	150
ii)	Cyclosporin (e.g. Cyclosporin 1.1, 1.2, 1.3, 1.11 or 1.36)	25 (dry weight value)
iii)	Ethanol (absolute)	50
iv)	Olive oil	ca. 237 to a
	total of	ca. 462.0

All ingredients are weighed directly into a stirring vessel. Ingredients (i) and (iii) are weighed in first. Ingredient (ii) is then added with continuous stirring until dissolution. Ingredient (iv) is thereafter added with stirring for a further 10 mins. The obtained solution is filtered through a Gelman Preflow Filter (400µm) at ca. 0.5 to 0.8 bar and filled into 50ml Rexo bottles. The bottles are sealed with a rubber cork and cap. The entire procedure is carried out under water-free conditions at room temperature with nitrogen gassing (0.25 bar) at all stages. The bottled solution, which is suitable for oral administration, comprises 50mg cyclosporin (dry weight)/ml. The solution may alternatively be filled into gelatin, e.g. hard or soft gelatin capsules as a means of taste masking.

Claims

1. A cyclosporin
(i) of formula II



(II)

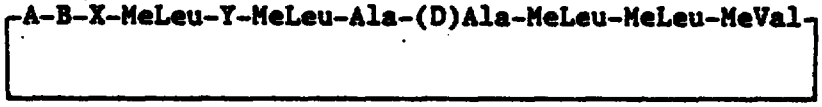
wherein
A is -3'-O-acetyl-MeBmt-
B is -αAbu-, -Thr-, -Val- or Nva-; and
when
B is -αAbu-,
X is -(D)Ala- and Y is -Val-;
when
B is -Thr- or -Val-,
X is -Sar- and Y is -Val-; or
when
B is -Nva-,
X is -Sar- and Y is -Val-, or
X is -(D)Ala- and Y is -Val-; or
wherein
A is -3'-O-acetyl-dihydro-MeBmt- or -cis-MeBmt-,

INGREDIENT		RELATIVE AMOUNT (g)
i)	Labrafil M 1944 CS	150
ii)	Cyclosporin (e.g. Cyclosporin 1.1, 1.2, 1.3, 1.11 or 1.36)	25 (dry weight value)
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	total of	ca. 462.0

All ingredients are weighed directly into a stirring vessel. Ingredients (i) and (iii) are weighed in first. Ingredient (ii) is then added with continuous stirring until dissolution. Ingredient (iv) is thereafter added with stirring for a further 10 mins. The obtained solution is filtered through a Gelman Preflow Filter (400µm) at ca. 0.5 to 0.8 bar and filled into 50ml Rexo bottles. The bottles are sealed with a rubber cork and cap. The entire procedure is carried out under water-free conditions at room temperature with nitrogen gassing (0.25 bar) at all stages. The bottled solution, which is suitable for oral administration, comprises 50mg cyclosporin (dry weight)/ml. The solution may alternatively be filled into gelatin, e.g. hard or soft gelatin capsules as a means of taste masking.

Claims

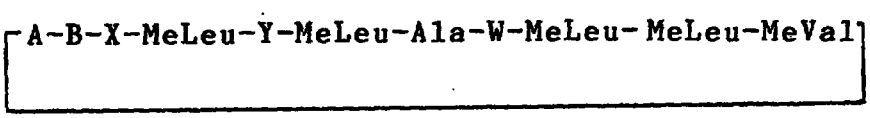
1. A cyclosporin
(i) of formula II



(II)

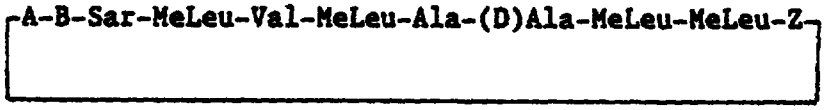
wherein
A is -3'-O-acetyl-MeBmt-
B is -αAbu-, -Thr-, -Val- or Nva-; and
when
B is -αAbu-,
X is -(D)Ala- and Y is -Val-;
when
B is -Thr- or -Val-,
X is -Sar- and Y is -Val-; or
when
B is -Nva-,
X is -Sar- and Y is -Val-, or
X is -(D)Ala- and Y is -Val-; or
wherein
A is -3'-O-acetyl-dihydro-MeBmt- or -cis-MeBmt-,

B is -αAbu-, X is -Sar- and Y is -Val-: or
ii) of formula II'



(II')

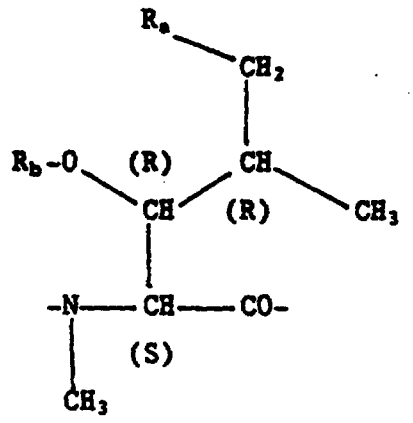
wherein
A is -3'-O-acyl-MeBmt- or -3'-O-acyl-dihydro-MeBmt- residue,
B is -αAbu-, -Thr-, -Val-, -Nva-, or the residue of a β-O-acyl-α-amino acid,
X is -Sar- or the residue of an optically active α-N-methylated α-amino acid residue having the (D)-configuration,
Y is -Val- or additionally, when B is -Nva-, -Nva-, and
W is the residue of a β-hydroxy- or β-O-acyl-α-amino acid having the (D)-configuration; or
iii) wherein the residue at the position 1-position is an -8'-C_{1-8}alkoxy-cis-MeBmt-or -dihydro-MeBmt- or -3'-O-acyl-8'-C_{1-8}alkoxy-cis-MeBmt- or -dihydro-MeBmt- residue; a -3'-O-acyl-cis-MeBmt-residue; a -7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt- or -3'-O-acyl-7'-desmethyl-7'-hydrocarbyl- -MeBmt- or -cis-MeBmt-residue wherein the hydrocarbyl moiety comprises at least two carbon atoms; or a -7'-desmethyl-7'-hydrocarbyl-dihydro-MeBmt- or -3'-O-acetyl-7'-desmethyl-7'-hydr ocarbyl-dihydro-MeBmt- residue wherein the hydrocarbyl moiety comprises at least two carbon atoms and wherein any aliphatic group or moiety as or comprising said hydrocarbyl moiety is saturated; or
(iv) wherein the 3'-carbon atom of the residue at the 1-position is oxo, C_{1-4}alkoxyimino, azidoalkyl-carbonyloxy or alkoxycarbonyloxy substituted, or wherein the β-carbon atom of the residue at the 2-position is β-oxo substituted or the residue at the 2-position is an (L)-isoleucyl residue; or
(v) of formula XI



(XI)

wherein
A is -N-desmethyl-dihydro-MeBmt, B is -Thr- and Z is -MeVal-, or
A is -dihydro-MeBmt-, B is -Thr- and Z is -Val-, or
A is -MeLeu-, B is -αAbu- and Z is -Val-; or which is
(vi) a dicarboxylic acid di-ester of a cyclosporin having a β-hydroxy-(L)-α-amino acid residue at the 2-position.

2. A cyclosporin according to claim 1 wherein the residue at the 1-position is a residue of formula XXI



(XXI)

wherein

R_a is -x'-y'-R_c in which

-x'-y'- is cis -CH=CH- or -CH_2-CH_2 and R_c is C_{2-9} alkoxymethyl or -x'-y' is cis or trans -CH=CH- or CH_2-CH_2- and R_c is hydrocarbyl having at least two carbon atoms, whereby, when -x'-y' is -CH_2-CH_2- any aliphatic group or moiety as or comprising R_c is saturated, and

R_b is hydrogen or acyl.

3. A cyclosporin according to claim 1 wherein the residue at the 1-position is -3'-desoxy-3'-oxo-MeBmt-, a -3'-desoxy-3'-(C_{1-4} alkoxyimino)-MeBmt- residue, a -3'-O-(C_{1-4} azidoalkyl)-carbonyl--MeBmt- or -dihydro-MeBmt- residue or a -3'-O-(C_{1-4}alkoxy)-carbonyl- -MeBmt- or -dihydro-MeBmt- residue, or wherein the residue at the 2-position is -α-methylketo-Gly- or -Ile-.

4. A cyclosporin according to claim 1 selected from the group consisting of:

1.3 [3'-O-acetyl-MeBmt]^1-[Thr]^2-Ciclosporin;
1.5 [3'-O-acetyl-MeBmt]^1-[Nva]^2-[Nva]^5-Ciclosporin;
1.6 [3'-O-acetyl-MeBmt]^1-[(D)Ala]^3-Ciclosporin;
1.7 [3'-O-acetyl-MeBmt]^1-[Nva]^2-[(D)Ala]^3-Ciclosporin;
1.10 [3'-O-acetyl-dihydro-MeBmt]^1-Ciclosporin;
1.11 [3'-O-methoxycarbonyl-MeBmt]^1-Ciclosporin;
1.12 [3'-O-(4-azidobutanoyl)-MeBmt]^1-Ciclosporin;
1.15 [3'-O-acetyl-MeBmt]^1-[O-acetyl-(D)Ser]^8-Ciclosporin;
1.16 [3'-O-acetyl-8'-methoxy-cis-MeBmt]^1-Ciclosporin;
1.17 [3'-O-acetyl-8'-t.butoxy-cis-MeBmt]^1-Ciclosporin;
1.18 [3'-O-acetyl-8'-methoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.19 [3'-O-acetyl-8'-t.butoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.20 [3'-O-acetyl-8'-methoxy-cis-MeBmt]^1-[Val]^2-Ciclosporin;
1.21 [3'-O-acetyl-8'-methoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporin;
1.22 [3'-O-acetyl-7'-desmethyl-7'-phenyl-MeBmt]^1-Ciclosporin;
1.23 [3'-O-acetyl-cis-MeBmt]^1-Ciclosporin;
1.24 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin;
1.25 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.26 [3'-O-acetyl-7'-desmethyl-7'-i.pentyl-cis-MeBmt]^1-Ciclosporin;
1.27 [3'-O-acetyl-7'-desmethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin;
1.28 [3'-O-acetyl-7'-desmethyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporin;
1.29 [3'-O-acetyl-7'-desmethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin;
1.30 [3'-O-acetyl-7'-desmethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin;
1.31 [3'-O-acetyl-7'-desmethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
1.32 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
1.33 [3'-O-acetyl-7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin;
1.34 [3'-O-acetyl-7'-desmethyl-7'-(3-bromo-n.propyl)-cis-MeBmt]^1-Ciclosporin;
1.36 1,2-ethanedicarboxylic acid-[O-threonyl]^2-Ciclosporin di-ester;
1.37 [3'-desoxy-3'-oxo-MeBmt]^1-Ciclosporin;
1.38 [3'-desoxy-3'-oxo-MeBmt]^1-[Val]^{2}Ciclosporin;
1.39 [3'-desoxy-3'-oxo-MeBmt]^1-[Nva]^{2}Ciclosporin;
1.40 [α-methylketo-Gly]^2-Ciclosporin;
1.41 [dihydro-MeBmt]^1-[α-methylketo-Gly]^2-Ciclosporin;
2.1 [3'-desoxy-3'-methoxyimino-MeBmt]^1-Ciclosporin;
2.2 [Ile]^2-Ciclosporin;
3.6 [N-desmethyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin;
3.8 [dihydro-MeBmt]^1-[Thr]^2-[Val]^{11}-Ciclosporin;
3.10 [MeLeu]^1-Ciclosporin;
4.1 [8'-methoxy-cis-MeBmt]^1-Ciclosporin;
4.2 [8'-t.butoxy-cis-MeBmt]^1-Ciclosporin;
4.3 [8'-methoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin;
4.4 [8'-t.butoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin;
4.5 [8'-methoxy-cis-MeBmt]^1-[Val]^2-Ciclosporin;
4.6 [8'-methoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporin;
4.7 [8'-methoxy-dihydro-MeBmt]^1-Ciclosporin;

4.8 [8'-methoxy-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin;
4.9 [8'-methoxy-dihydro-MeBmt]^1-[Val]^2-Ciclosporin;
4.10 [8'-methoxy-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin;
6.1 [7'-desmethyl-7'-phenyl-MeBmt]^1-Ciclosporin;
6.2 [7'-desmethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin;
6.3 [7'-desmethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin;
6.4 [7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Thr]^2-Ciclosporin;
6.5 [7'-desmethyl-7'-(3-methyl-n.butyl-cis-MeBmt]^1-Ciclosporin;
6.6 [7'-desmethyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporin;
6.7 [7'-desmethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin;
6.8 [7'-desmethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin;
6.9 [7'-desmethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
6.10 [7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin;
6.11 [7'-desmethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin;
6.12 [7'-desmethyl-7'-(3-bromo-n.propyl-cis-MeBmt]^1-Ciclosporin;
6.13 [7'-desmethyl-7'-phenyl-dihydro-MeBmt]^1-Ciclosporin;
6.14 [7'-desmethyl-7'-n.propyl-dihydro-MeBmt]^1-Ciclosporin;
6.15 [7'-desmethyl-7'-ethyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin;
6.16 [7'-desmethyl-7'-(3-methyl-n.butyl)-dihydro-MeBmt]^1-Ciclosporin;
6.17 [7'-desmethyl-7'-i.propyl-dihydro-MeBmt]^1-Ciclosporin;
6.18 [7'-desmethyl-7'-ethyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporin;
6.19 [7'-desmethyl-7'-ethyl-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin;
6.20 [7'-desmethyl-7'-phenyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporin;
6.21 [7'-desmethyl-7'-ethyl-dihydro-MeBmt]^1-Ciclosporin;

5. A pharmaceutical composition comprising a cyclosporin as claimed in any one of claims 1 to 4, together with a pharmaceutically acceptable diluent or carrier therefore.

6. A cyclosporin as claimed in any one of claims 1 to 4 for use as a pharmaceutical.

7. Use of a cyclosporin
(i) wherein the 3'-carbon atom of the residue at the 1-position or the β-carbon atom of the residue at the 2-position is O-acyl or oxo substituted, or
(ii) wherein the 3'-carbon atom of the residue at the 1-position is C_{1-4}alkoxyimino substituted, wherein the residue at the 2-position is an (L)-isoleucyl residue, or the residue at the 11-position is an N-methyl-(L)-alanyl, N-methyl-(L)-isoleucyl or N-methyl-(L)-alloisoleucyl residue; or
(iii) of formula XI as illustrated in claim 1 wherein:
Z is -Val- or -MeVal-:
when
Z is -Val-,
A i s -MeBmt- or -dihydro-MeBmt-; or
when
Z is -MeVal-
A is -3'-desoxy-MeBmt-, -3'-desoxy-dihydro-MeBmt-, -N-desmethyl-MeBmt-, -N-desmethyl-dihydro-MeBmt, -3'-desoxy-4'-desmethyl-dihydro-MeBmt- or -MeLeu-: and
when
Z is -Val-,
B is -αAbu- or -Thr-;
when
Z is -MeVal- and
A is -3'-desoxy-MeBmt-, -3'-desoxy-dihydro-MeBmt-, -3'-desoxy--4'-desmethyl-dihydro-MeBmt- or -MeLeu-,
B is -αAbu-; or
when
Z is -MeVal- and
A is -N-desmethyl-MeBmt- or -N-desmethyl-dihydro-MeBmt-,
B is -Thr-;
in the manufacture of a medicament for improving or increasing the efficacy of, or increasing

* C L M S *

sensitivity to, other chemotherapeutic drug therapy, or for reducing effective chemotherapeutic dosage rate for a second chemotherapeutic drug substance, or
for an adjuvant in treating morbid conditions characterised by resistance to a second chemotherapeutic drug substance, or for enhancing or improving chemotherapeutic treatment of morbid conditions exhibiting or characterised by resistance to said treatment, or
for reversing or reducing resistance to chemotherapeutic treatment, or
for restoring sensitivity to chemotherapeutic treatment, or
for an adjuvant to other chemotherapeutic drug therapy.

8. A cyclosporin according to claim 7 which is a cyclosporin as defined under any one of (i), (ii), (iv), (v) or (vi) of claim 1 or a cyclosporin as defined under (iii) of claim 1 wherein the residue at the 1-position is a 3'-O-acyl substituted.

9. A cyclosporin according to claim 7 selected from the group consisting of:
1.1 [3'-O-acetyl-MeBmt]^1-Ciclosporin;
1.4 [3'-O-acetyl-MeBmt]^1-[Nva]^2-Ciclosporin;
1.8 [3'-O-acetyl-MeBmt]^1-[(D)MeVal]^{11}-Ciclosporin;
1.9 [3'-O-acetyl-MeBmt]^1-[Val]^{11}-Ciclosporin;
1.13 [3'-O-acetyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.14 [3'-O-acetyl-N-desmethyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
1.35 [O-acetyl-Thr]^2-Ciclosporin;
2.3 [MeAla]^{11}-Ciclosporin;
2.4 [MeIle]^{11}-Ciclosporin;
2.5 [MeAlloIle]^{11}-Ciclosporin;
2.6 [MeLeu]^{11}-Ciclosporin;
3.1 [Val]^{11}-Ciclosporin;
3.2 [dihydro-MeBmt]^1-[Val]^{11}-Ciclosporin;
3.3 [3'-desoxy-MeBmt]^1-Ciclosporin;
3.4 [3'-desoxy-dihydro-MeBmt]^1-Ciclosporin;
3.5 [N-desmethyl-MeBmt]^1-[Thr]^2-Ciclosporin;
3.7 [Thr]^2-[Val]^{11}-Ciclosporin;
3.9 [3'-desoxy-4'-desmethyl-dihydro-MeBmt]^1-Ciclosporin;
and individual cyclosporins 1.2 through 1.41, 2.1 and 2.2, and 3.6 through 3.10 of claim 4.

10. A pharmaceutical composition comprising a cyclosporin of structure as defined in any one of claims 7 to 9, together with a pharmaceutically acceptable diluent or carrier therefor.

11. A cyclosporin wherein the residue at the 1-position is -5'-des-(1-propenyl)-5'-formyl-MeBmt- in free or 3'-O-protected form.

12. A cyclosporin according to claim 11 selected from the group consisting of:
5.1 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-Ciclosporin;
5.2 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin;
5.3 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Val]^2-Ciclosporin; and
5.4 [3'-O-acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Nva]^2-Ciclosporin.

13. A cyclosporin wherein the residue at the 1-position is a [3'-desoxy-3'-oxo-MeBmt] residue.

14. [3'-desoxy-3'-oxo-MeBmt]^1-[Val]^2- Ciclosporin.

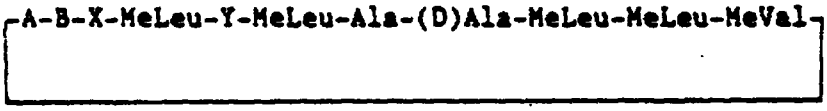
15. A pharmaceutical composition comprising the compound of claim 13, together with a pharmaceutically acceptable diluent or carrier.

16. The compound of claim 14 for use as a pharmaceutical.

Patentansprüche

1. Cylosporin

(i) der Formel II



(II)

worin

A für -3'-O-Acetyl-MeBmt- steht

B für -αAbu-, -Thr-, -Val- oder -Nva- steht, und

wenn

B für -αAbu- steht, dann steht

X für -Sar- und Y für -Val-,

wenn

B für -Thr- oder -Val- steht, dann steht

X für -Sar- und Y für -Val-, oder

wenn

B für -Nva- steht, dann steht

X für -Sar- und Y für -Nva-, oder dann steht

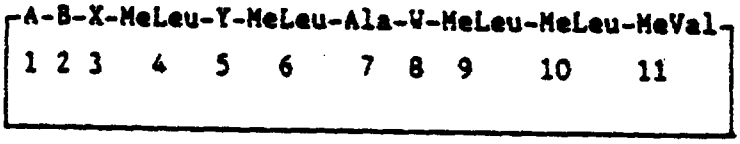
X für -(D)Ala und Y für -Val, oder

worin

A für -3'-O-Acetyldihydro-MeBmt- oder -cis-MeBmt- steht,

B für -αAbu- steht, X für -Sar- steht und Y für -Val-steht, oder

(ii) der Formel II'



(II')

worin

A für einen -3'-O-Acyl-MeBmt- Rest oder -3'-O-Acyldihydro-MeBmt-Rest steht,

B für -αAbu-, -Thr, -Val-, -Nva- oder für den Rest einer β-O-Acyl-α-aminosäure steht,

X für -Sar- oder den Rest eines optisch aktiven α-N-methylierten α-Aminosäurerests steht, der (D)-Konfiguration aufweist,

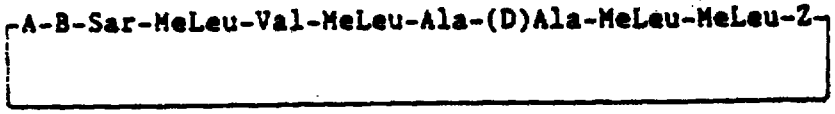
Y für -Val- steht oder zusätzlich für -Nva- steht, wenn B für - Nva- steht, und

W für den Rest einer β-Hydroxy- oder β-O-Acyl-α-aminosäure steht, die (D)-Konfiguration aufweist, oder

(iii) worin der Rest an Position 1 für einen -8'-C_{1-8}Alkoxy-cis-MeBmt- oder -dihydro-MeBmt- oder 3'-O-Acyl-8'-C_{1-8}alkoxy-cis-MeBmt- oder -dihydro-MeBmt- Rest steht, für einen -3'-O-Acyl-cis-MeBmt-Rest steht, für einen -7'-Demethyl-7'-hydrocarbyl-MeBmt- oder -cis-MeBmt- oder einen -3'-O-Acyl-7'-demethyl-7'-hydrocarbyl- -MeBmt- oder -cis-MeBmt- Rest steht, worin der Hydroxycarbylrest mindestens zwei Kohlenstoffatome aufweist, oder für einen -7'-Demethyl-7'-hydrocarbyl-dihydro-MeBmt- oder -3'-O-Acyl-7'-demethyl-7'-hydrocarbyl-dihydro-MeBmt- Rest steht, worin der Hydroxycarbylrest mindestens zwei Konlenstoffatome aufweist und worin jede aliphtische Gruppe oder jeder aliphatische Rest, wie dieser Hydrocarbylteil oder diesen Hydrocarbylteil enthaltend, gesättigt ist, oder

(iv) worin das 3'-Kohlenstoffatom des Rests an der Position 1 Oxo-, C_{1-4}Alkoxyimino-, Azidoalkylcarbonyloxy- oder Alkoxycarbonyloxy-substituiert ist, oder worin das β-Kohlenstoffatom des Rests an der Position 2 β-Oxo-substituiert ist oder der Rest an der Position 2 einen (L)-Isoleucylrest steht, oder

(v) der Formel XI

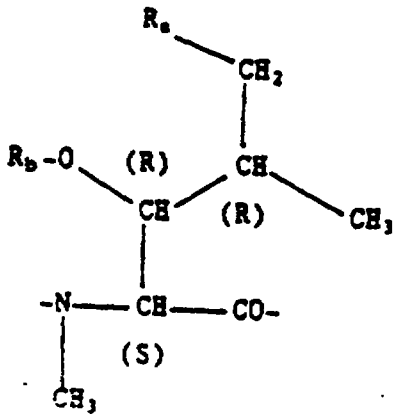


(XI)

worin

A für -N-Demethyldihydro-MeBmt- steht, B für -Thr- steht und Z für -MeVal- steht, oder
A für -dihydro-MeBmt- steht, B für -Thr- steht und Z für -Val-steht, oder
A für -MeLeu- steht, B für -αAbu- steht und Z für -Val- steht, oder das folgendes ist
(iv) ein Dicarbonsäurediester eines Cyclosporins, das einen β-Hydroxy-(L)-aminosäurerest an der Position 2 aufweist.

2. Cyclosporin gemäß Anspruch 1, worin der Rest an der Position 1 ein Rest der Formel XXI ist



(XXI)

worin

R_a für -x'-y'-R_c steht, worin
-x'-y'- für cis-CH=CH- oder -CH_2-CH_2- steht und R_c für C_{2-9} Alkoxymethyl steht oder -x'-y'- für cis- oder für trans-CH=CH- oder für -CH_2-CH_2- steht und R_c für Hydrocarbyl steht, das mindestens zwei Kohlenstoffatome aufweist, wobei, wenn -x'-y'-für -CH_2-CH_2- steht, jede aliphatische Gruppe oder jeder aliphatische Teil, wie R_c oder R_c enthaltend, gesättigt ist, und
R_b für Wasserstoff oder Acyl steht.

3. Cyclosporin gemäß Anspruch 1, worin der Rest an der Position 1 für -3'-Desoxy-3'-oxo-MeBmt-, einen 3'-Desoxy-3'-(C_{1-4}-alkoxyimino)-MeBmt- Rest, einen -3'-O-(C_{1-4}Acidoalkyl)-carbonyl-MeBmt- oder dihydro-MeBmt Rest steht oder für einen -3'-O-(C_{1-4}Alkoxy)-carbonyl--MeBmt- oder -dihydro-MeBmt-Rest steht, oder worin der Rest an der Position 2 für -α-Methylketo-Gly- oder -Ile- steht.

4. Cyclosporin gemäß Anspruch 1, ausgewählt aus der Gruppe, die besteht aus
1.3 [3'-O-Acetyl-MeBmt]^1-[Thr]^2-Ciclosporin,
1.5 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-[Nva]^5-Ciclosporin,
1.6 [3'-O-Acetyl-MeBmt]^1-[(D)Ala]^3-Ciclosporin,
1.7 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-[(D)Ala]^3-Ciclosporin,
1.10 [3'-O-Acetyl-dihydro-MeBmt]^1-Ciclosporin,
1.11 [3'-O-Methoxycarbonyl-MeBmt]^1-Ciclosporin,
1.12 [3'-O-(4-Azidobutanoyl)-MeBmt]^1-Ciclosporin,
1.13 [3'-O-Acetyl-MeBmt]^1-[O-acetyl-(D)Ser]^8-Ciclosporin,
1.16 [3'-O-Acetyl-8'-methoxy-cis-MeBmt]^1-Ciclosporin,
1.17 [3'-O-Acetyl-8'-t-butoxy-cis-MeBmt]^1-Ciclosporin,
1.18 [3'-O-Acetyl-8'-methoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin

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1.19 [3'-O-Acetyl-8'-t-butoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin
1.20 [3'-O-Acetyl-8'-methoxy-cis-MeBmt]^1-[Val]^2-Ciclosporin,
1.21 [3'-O-Acetyl-8'-methoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporin,
1.22 [3'-O-Acetyl-7'-demethyl-7'-phenyl-MeBmt]^1-Ciclosporin,
1.23 [3'-O-Acetyl-cis-MeBmt]^1-Ciclosporin,
1.24 [3'-O-Acetyl-7'-demethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin,
1.25 [3'-O-Acetyl-7'-demethyl-7'-vinyl-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin,
1.26 [3'-O-Acetyl-7'-demethyl-7'-i-pentyl-cis-MeBmt]^1-Ciclosporin,
1.27 [3'-O-Acetyl-7'-demethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin,
1.28 [3'-O-Acetyl-7'-demethyl-7'-n-propyl-cis-MeBmt]^1-Ciclosporin,
1.29 [3'-O-Acetyl-7'-demethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin,
1.30 [3'-O-Acetyl-7'-demethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin,
1.31 [3'-O-Acetyl-7'-demethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin,
1.32 [3'-O-Acetyl-7'-demethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin,
1.33 [3'-O-Acetyl-7'-demethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin,
1.34 [3'-O-Acetyl-7'-demethyl-7'-(3-brom-n-propyl)-cis-MeBmt]^1-Ciclosporin,
1.36 [1,2-Ethandicarbonsäure-[O-threonyl]^2-Ciclosporindiester,
1.37 [3'-Desoxy-3'-oxo-MeBmt]^1-Ciclosporin,
1.38 [3'-Desoxy-3'-oxo-MeBmt]^1-[Val]^2-Ciclosporin,
1.39 [3'-Desoxy-3'-oxo-MeBmt]^1-[Nva]^2-Ciclosporin,
1.40 [α-Methylketo-Gly]^2-Ciclosporin,
1.41 [Dihydro-MeBmt]^1-[α-methylketo-Gly]^2-Ciclosporin,
2.1 [3'-Desoxy-3'-methoxyimino-MeBmt]^1-Ciclosporin,
2.2 [Ile]^2-Ciclosporin,
3.6 [N-Demethyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin,
3.8 [Dihydro-MeBmt]^1-[Thr]^2-[Val]^{11}-Ciclosporin,
3.10 [MeLeu]^1-Ciclosporin,
4.1 [8'-Methoxy-cis-MeBmt]^1-Ciclosporin,
4.2 [8'-t-butoxy-cis-MeBmt]^1-Ciclosporin,
4.3 [8'-Methoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin,
4.4 [8'-t-butoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporin,
4.5 [8'-Methoxy-cis-MeBmt]^1-[Val]^2-Ciclosporin,
4.6 [8'-Methoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporin,
4.7 [8'-Methoxy-dihydro-MeBmt]^1-Ciclosporin,
4.8 [8'-Methoxy-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin,
4.9 [8'-Methoxy-dihydro-MeBmt]^1-[Val]^2-Ciclosporin,
4.10 [8'-Methoxy-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin,
6.1 [7'-Demethyl-7'-phenyl-MeBmt]^1-Ciclosporin,
6.2 [7'-Demethyl-7'-phenyl-cis-MeBmt]^1-Ciclosporin,
6.3 [7'-Demethyl-7'-vinyl-cis-MeBmt]^1-Ciclosporin,
6.4 [7'-Demethyl-7'-vinyl-cis-MeBmt]^1-[Thr]^2-Ciclosporin,
6.5 [7'-Demethyl-7'-(3-methyl-n-butyl)-cis-MeBmt]^1-Ciclosporin,
6.6 [7'-Demethyl-7'-n-propyl-cis-MeBmt]^1-Ciclosporin,
6.7 [7'-Demethyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporin,
6.8 [7'-Demethyl-7'-phenyl-MeBmt]^1-[Val]^2-Ciclosporin,
6.9 [7'-Demethyl-7'-phenyl-cis-MeBmt]^1-[Val]^2-Ciclosporin,
6.10 [7'-Demethyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporin,
6.11 [7'-Demethyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporin,
6.12 [7'-Demethyl-7'-(3-brom-n-propyl)-cis-MeBmt]^1-Ciclosporin,
6.13 [7'-Demethyl-7'-phenyl-dihydro-MeBmt]^1-Ciclosporin,
6.14 [7'-Demethyl-7'-n-propyl-dihydro-MeBmt]^1-Ciclosporin,
6.15 [7'-Demethyl-7'-ethyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporin,
6.16 [7'-Demethyl-7'-(3-methyl-n-butyl)-dihydro-MeBmt]^1-Ciclosporin,
6.17 [7'-Demethyl-7'-i-propyl-dihydro-MeBmt]^1-Ciclosporin,
6.18 [7'-Demethyl-7'-ethyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporin,
6.19 [7'-Demethyl-7'-ethyl-dihydro-MeBmt]^1-[Nva]^2-Ciclosporin,
6.20 [7'-Demethyl-7'-phenyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporin,
6.21 [7'-Demethyl-7'-ethyl-dihydro-MeBmt]^1-Ciclosporin.

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5. Pharmazeutische Zusammensetzung, die ein Cyclosporin gemäß einem der Ansprüche 1 bis 4 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger hierfür enthält.

6. Cyclosporin gemäß einem der Ansprüche 1 bis 4 zur Verwendung als Pharmazeutikum.

7. Verwendung eines Cyclosporins
(i) worin das 3'-Kohlenstoffatom des Rests an der Position 1 oder das β-Kohlenstoffatom des Rests an der Position 2 O-Acyl- oder Oxo-substituiert ist, oder
(ii) worin das 3'-Kohlenstoffatom des Rests an der Position 1 C_{1-4}-Alkoxyimino-substituiert ist, worin der Rest an der Position 2 ein (L)-Isoleucylrest ist, oder der Rest an der Position 11 ein N-Methyl-(L)-alanyl-, N-Methyl-(L)-isoleucyl- oder N-Methyl-(L)-alloisoleucylrest ist, oder
(iii) der Formel XI, wie in Anspruch 1 gezeigt, worin
Z für -Val- oder -MeVal- steht, wenn
Z für -Val- steht, dann steht
A für -MeBmt- oder -dihydro-MeBmt-, oder wenn
Z für -MeVal- steht, dann steht
A für -3'-Desoxy-MeBmt-, -3'-Desoxy-dihydro-MeBmt-, -N-Demethyl-MeBmt-, -N-Demethyl-dihydro-MeBmt-, -3'-Desoxy-4'-demethyl-dihydro-MeBmt- oder -MeLeu-, und wenn
Z für -Val- steht, dann steht
B für -αAbu- oder -Thr-, wenn
Z für -MeVal- steht und
A für -3'-Desoxy-MeBmt-, -3'-Desoxy-dihydro-MeBmt-, -3'-Desoxy-4'-demethyl-dihydro-MeBmt- oder -MeLeu- steht, dann steht
B für -αAbu-, oder wenn
Z für -MeVal- steht und
A für -N-Demethyl-MeBmt- oder -N-Demethyl-dihydro-MeBmt-steht, dann steht
B für -Thr-,
zur Herstellung eines Arzneimittels zur Verbesserung oder Steigerung der Wirkung von einer oder zur Steigerung der Empfindlichkeit gegenüber einer anderen Therapie mit einem chemotherapeutischen Medikament oder zur Reduzierung der wirksamen chemotherapeutischen Dosierungsmenge eines zweiten chemotherapeutischen Arzneimittels oder als Adjuvans zur Behandlung von durch Resistenz gegenüber einem zweitem chemotherapeutischen Arzneimittel gekennzeichneten Krankheitszuständen oder zur Steigerung oder Verbesserung einer chemotherapeutischen Behandlung von Krankheitszuständen, die Resistenz gegenüber diesr Behandlung zeigen oder dadurch gekennzeichnet sind oder zur Aufhebung oder Reduzierung einer Resistenz gegenüber einer chemotherapeutischen Behandlung oder zur Wiederherstellung der Empfindlichkeit gegenüber einer chemotherapeutischen Behandlung oder als Adjuvans bei einer anderen Therapie mit chemotherapeutischen Arzneimitteln.

8. Cyclosporin gemäß Anspruch 7, das ein Cyclosporin, wie unter einem der Punkte (i), (ii), (iv), (v) oder (vi) nach Anspruch 1 definiert, ist oder ein Cyclosporin ist, wie unter (iii) nach Anspruch 1d definiert, worin der Rest an der Position 1 ein 3'-O-Acyl-substituierter Rest ist.

9. Cyclosporin gemäß Anspruch 7, ausgewählt aus der Gruppe, die besteht aus
1.1 [3'-O-Acetyl-MeBmt]^1-Ciclosporin,
1.4 [3'-O-Acetyl-MeBmt]^1-[Nva]^2-Ciclosporin,
1.8 [3'-O-Acetyl-MeBmt]^1-[(D)MeVal]^{11}-Ciclosporin,
1.9 [3'-O-Acetyl-MeBmt]^1-[Val]^{11}-Ciclosporin,
1.13 [3'-O-Acetyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin,
1.14 [3'-O-Acetyl-N-demethyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin,
1.35 [O-Acetyl-Thr]^2-Ciclosporin,
2.3 [MeAla]^{11}-Ciclosporin,
2.4 [MeIle]^{11}-Ciclosporin,
2.5 [MeAlloIle]^{11}-Ciclosporin,
2.6 [MeLeu]^{11}-Ciclosporin,
3.1 [Val]^{11}-Ciclosporin,
3.2 [Dihydro-MeBmt]^1-[Val]^{11}-Ciclosporin,

3.3 [3'-Desoxy-MeBmt]^1-Ciclosporin,
3.4 [3'-Desoxy-dihydro-MeBmt]^1-Ciclosporin,
3.5 [N-Demethyl-MeBmt]^1-[Thr]^2-Ciclosporin,
3.7 [Thr]^2-[Val]^{11}-Ciclosporin,
3.9 [3'-Desoxy-4'-demethyl-dihydro-MeBmt]^1-Ciclosporin,
und die einzelnen Cyclosporine 1.2 bis 1.41, 2.1 und 2.2 und 3.6 bis 3.10 nach Anspruch 4.

10. Pharmazeutische Zusammensetzung, die ein Cyclosporin mit einer in einem der Ansprüche 7 bis 9 definierten Struktur, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger hierfür enthält.

11. Cyclosporin, worin der Rest an der Position 1 -5'-Des-(1-propenyl)-5'-formyl-MeBmt- in freier oder 3'-O-geschützter Form ist.

12. Cyclosporin gemäß Anspruch 11, ausgewählt aus der Gruppe, die besteht aus
5.1 [3'-O-Acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-Ciclosporin,
5.2 [3'-O-Acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporin,
5.3 [3'-O-Acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Val]^2-Ciclosporin und
5.4 [3'-O-Acetyl-5'-des-(1-propenyl)-5'-formyl-MeBmt]^1-[Nva]^2-Ciclosporin.

13. Cyclosporin, worin der Rest an der Position 1 ein [3'-Desoxy-3'-oxo-MeBmt] Rest ist.

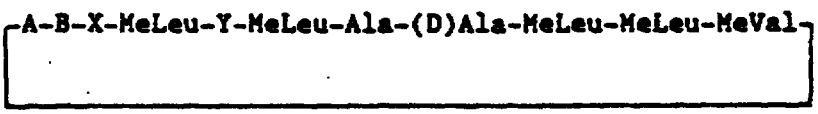
14. [3'-Desoxy-3'-oxo-MeBmt]^1-[Val]^2-Ciclosporin.

15. Pharmazeutische Zusammensetzung, die die Verbindung gemäß Anspruch 13 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger hierfür enthält.

16. Verbindung nach Anspruch 14 zur Verwendung als Pharmazeutikum.

Revendications

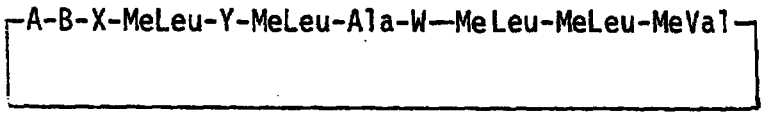
1. Une cyclosporine
(i) de formule II



(II)

dans laquelle
A signifie -3'-O-acétyl-MeBmt-
B signifie -αAbu-, -Thr-, -Val- ou -Nva-; et
lorsque
B signifie -αAbu-,
X signifie -(D)Ala- et Y signifie -Val-;
lorsque
B signifie -Thr- ou -Val-,
X signifie -Sar- et Y signifie -Val-; ou
lorsque
B signifie -Nva-,
X signifie -Sar- et Y signifie -Nva-, ou
X signifie -(D)Ala- et Y signifie -Val-; ou
dans laquelle
A signifie -3'-O-acétyl-dihydro-MeBmt- ou -cis-MeBmt-,
B signifie -αAbu-, X signifie -Sar- et Y signifie -Val-,
ou

ii) de formule II'



(II')

dans laquelle

A signifie un reste -3'-O-acyl-MeBmt- ou 3'-O-acyl-dihydro-MeBmt-,

B signifie αAbu-, -Thr-, -Val-, -Nva- ou le reste d'un β-O-acyl-α-amino-acide,

X signifie -Sar- ou le reste d'un α-amino-acide α-N-méthylé optiquement actif ayant la configuration (D),

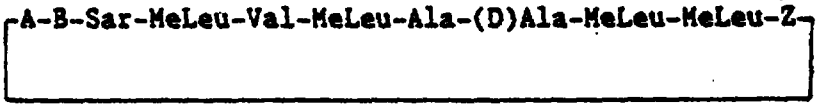
Y signifie -Val- ou, lorsque B signifie -Nva-, également -Nva-, et

W signifie le reste d'un β-hydroxy- ou β-O-acyl-α-amino-acide ayant la configuration (D), ou

iii) dans laquelle le reste en position 1 est un reste -8'-C_{1-8}alcoxy- -cis-MeBmt- ou dihydro-MeBmt- ou -3'-O-acyl-8'-C_{1-8}alcoxy- -cis-MeBmt- ou -dihydro-MeBmt-; un reste -3'-O-acyl-cis-MeBmt-; un reste -7'-déméthyl-7'-hydrocarbyl- -MeBmt- ou -cis-MeBmt- ou -3'-O-acyl-7'-déméthyl-7'-hydrocarbyl- -MeBmt- ou -cis-MeBmt- dans lesquels le fragment hydrocarbyle comprend au moins deux atomes de carbone; ou un reste -7'-déméthyl-7'-hydrocarbyl-dihydro-MeBmt- ou -3'-O-acétyl-7'-déméthyl-7'-hydrocarbyl-dihydro-MeBmt- dans lesquels le fragment hydrocarbyle comprend au moins deux atomes de carbone et dans lesquels tout groupe ou fragment aliphatique en tant que dit reste hydrocarbyle ou comprenant ledit reste hydrocarbyle est saturé; ou

(iv) dans laquelle l'atome de carbone 3' du reste en position 1 est substitué par un groupe oxo, C_{1-4}-alcoxyimino, azidoalkylcarbonyloxy ou alcoxycarbonyloxy, ou dans laquelle l'atome de carbone β du reste en position 2 est substitué par un groupe β-oxo ou dans laquelle le reste en position 2 signifie un reste (L-)isoleucyle; ou

(v) de formule XI



(XI)

dans laquelle

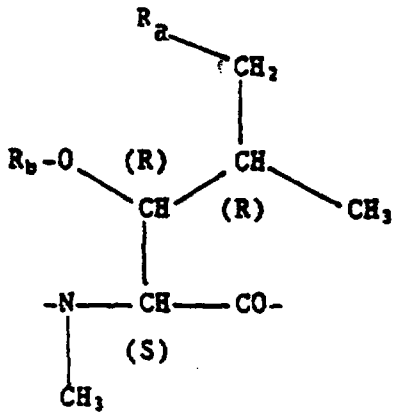
A signifie -N-déméthyl-dihydro-MeBmt-, B signifie -Thr-et Z signifie -MeVal-, ou

A signifie -dihydro-MeBmt-, B signifie -Thr- et Z signifie -Val-, ou

A signifie -MeLeu-, B signifie -αAbu- et Z signifie -Val-; ou qui est

(v) un di-ester d'acide dicarboxylique d'une cyclosporine ayant en position 2 un reste de β-hydroxy-(L)-α-amino-acide.

2. Une cyclosporine selon la revendication 1, dans laquelle le reste en position 1 est un reste de formule XXI



(XXI)

dans laquelle
R_a signifie -x'-y'-R_c où
-x'-y'- signifie -CH=CH- cis ou -CH_2-CH_2- et R_c signifie C_{2-9}alcoxyméthyle, ou bien -x'-y'- signifie -CH=CH- cis ou trans ou -CH_2-CH_2- et R_c signifie un reste hydrocarbyle ayant au moins deux atomes de carbone, tout groupe ou fragment aliphatique en tant que R_c ou comprenant R_c étant saturé lorsque -x'-y'-signifie -CH_2-CH_2-, et
R_b signifie l'hydrogène ou un groupe acyle.

3. Une cyclosporine selon la revendication 1, dans laquelle le reste en position 1 est un reste -3'-désoxy-3'-oxo-MeBmt-, -3'-désoxy-3'-(C_{1-4}-alcoxyimino)-MeBmt-, -3'-O-(C_{1-4} azidoalkyl)-carbonyl- -MeBmt- ou -dihydro-MeBmt- ou -3'-O-(C_{1-4}alcoxy)-carbonyl- -MeBmt- ou -dihydro-MeBmt-, ou dans laquelle le reste en position 2 signifie α-méthylcéto-Gly- ou -Ile-.

4. Une cyclosporine selon la revendication 1, choisie dans le groupe constitué par les cyclosporines suivantes :
   1.3 [3'-O-acétyl-MeBmt]^1-[Thr]^2-Ciclosporine;
   1.5 [3'-O-acétyl-MeBmt]^1-[Nva]^2-[Nva]^5-Ciclosporine;
   1.6 [3'-O-acétyl-MeBmt]^1-[(D)Ala]^3-Ciclosporine;
   1.7 [3'-O-acétyl-MeBmt]^1-[Nva]^2-[(D)Ala]^3-Ciclosporine;
   1.10 [3'-O-acétyl-dihydro-MeBmt]^1-Ciclosporine;
   1.11 [3'-O-méthoxycarbonyl-MeBmt]^1-Ciclosporine;
   1.12 [3'-O-(4-azidobutanoyl)-MeBmt]^1-Ciclosporine;
   1.13 [3'-O-acétyl-MeBmt]^1-[O-acétyl-(D)Ser]^8-Ciclosporine;
   1.16 [3'-O-acétyl-8'-methoxy-cis-MeBmt]^1-Ciclosporine;
   1.17 [3'-O-acétyl-8'-t.butoxy-cis-MeBmt]^1-Ciclosporine;
   1.18 [3'-O-acétyl-8'-méthoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporine;
   1.19 [3'-O-acétyl-8'-t.butoxy-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporine;
   1.20 [3'-O-acétyl-8'-méthoxy-cis-MeBmt]^1-[Val]^2-Ciclosporine;
   1.21 [3'-O-acétyl-8'-méthoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporine;
   1.22 [3'-O-acétyl-7'-déméthyl-7'-phényl-MeBmt]^1-Ciclosporine;
   1.23 [3'-O-acétyl-cis-MeBmt]^1-Ciclosporine;
   1.24 [3'-O-acétyl-7'-déméthyl-7'-vinyl-cis-MeBmt]^1-Ciclosporine;
   1.25 [3'-O-acétyl-7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[O-acetyl-Thr]^2-Ciclosporine;
   1.26 [3'-O-acétyl-7'-déméthyl-7'-i.pentyl-cis-MeBmt]^1-Ciclosporine;
   1.27 [3'-O-acétyl-7'-déméthyl-7'-phényl-cis-MeBmt]^1-Ciclosporine;
   1.28 [3'-O-acétyl-7'-déméthyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporine;
   1.29 [3'-O-acétyl-7'-déméthyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporine;
   1.30 [3'-O-acétyl-7'-déméthyl-7'-phényl-MeBmt]^1-[Val]^2-Ciclosporine;
   1.31 [3'-O-acétyl-7'-déméthyl-7'-phényl-cis-MeBmt]^1-[Val]^2-Ciclosporine;
   1.32 [3'-O-acétyl-7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporine;
   1.33 [3'-O-acétyl-7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporine;
   1.34 [3'-O-acétyl-7'-déméthyl-7'-(3-bromo-n.propyl)-cis-MeBmt]^1-Ciclosporine;
   1.36 di-ester de l'acide 1,2-éthanedicarboxylique et de la [O-thréonyl]^2-Cyclosporine;

1.37 [3'-désoxy-3'-oxo-MeBmt]^1-Ciclosporine;
1.38 [3'-désoxy-3'-oxo-MeBmt]^1-[Val]^{2}Ciclosporine;
1.39 [3'-désoxy-3'-oxo-MeBmt]^1-[Nva]^{2}Ciclosporine;
1.40 [α-méthylcéto-Gly]^2-Ciclosporine;
1.41 [dihydro-MeBmt]^1-[α-méthylcéto-Gly]^2-Ciclosporine;
2.1 [3'-désoxy-3'-méthoxyimino-MeBmt]^1-Ciclosporine;
2.2 [Ile]^2-Ciclosporine;
3.6 [N-déméthyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporine;
3.8 [dihydro-MeBmt]^1-[Thr]^2-[Val]^{11}-Ciclosporine;
3.10 [MeLeu]^1-Ciclosporine;
4.1 [8'-méthoxy-cis-MeBmt]^1-Ciclosporine;
4.2 [8'-t.butoxy-cis-MeBmt]^1-Ciclosporine;
4.3 [8'-méthoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporine;
4.4 [8'-t.butoxy-cis-MeBmt]^1-[Thr]^2-Ciclosporine;
4.5 [8'-méthoxy-cis-MeBmt]^1-[Val]^2-Ciclosporine;
4.6 [8'-méthoxy-cis-MeBmt]^1-[Nva]^2-Ciclosporine;
4.7 [8'-méthoxy-dihydro-MeBmt]^1-Ciclosporine;
4.8 [8'-méthoxy-dihydro-MeBmt]^1-[Thr]^2-Ciclosporine;
4.9 [8'-méthoxy-dihydro-MeBmt]^1-[Val]^2-Ciclosporine;
4.10 [8'-méthoxy-dihydro-MeBmt]^1-[Nva]^2-Ciclosporine;
6.1 [7'-déméthyl-7'-phényl-MeBmt]^1-Ciclosporine;
6.2 [7'-déméthyl-7'-phényl-cis-MeBmt]^1-Ciclosporine;
6.3 [7'-déméthyl-7'-vinyl-cis-MeBmt]^1-Ciclosporine;
6.4 [7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[Thr]^2-Ciclosporine;
6.5 [7'-déméthyl-7'-(3-méthyl-n.butyl)-cis-MeBmt]^1-Ciclosporine;
6.6 [7'-déméthyl-7'-n.propyl-cis-MeBmt]^1-Ciclosporine;
6.7 [7'-déméthyl-7'-(β-allyl)-cis-MeBmt]^1-Ciclosporine;
6.8 [7'-déméthyl-7'-phényl-MeBmt]^1-[Val]^2-Ciclosporine;
6.9 [7'-déméthyl-7'-phényl-cis-MeBmt]^1-[Val]^2-Ciclosporine;
6.10 [7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[Val]^2-Ciclosporine;
6.11 [7'-déméthyl-7'-vinyl-cis-MeBmt]^1-[Nva]^2-Ciclosporine;
6.12 [7'-déméthyl-7'-(3-bromo-n.propyl)-cis-MeBmt]^1-Ciclosporine:
6.13 [7'-déméthyl-7'-phényl-dihydro-MeBmt]^1-Ciclosporine:
6.14 [7'-déméthyl-7'-n.propyl-dihydro-MeBmt]^1-Ciclosporine;
6.15 [7'-déméthyl-7'-éthyl-dihydro-MeBmt]^1-[Thr]^2-Ciclosporine;
6.16 [7'-déméthyl-7'-(3-méthyl-n.butyl)-dihydro-MeBmt]^1-Ciclosporine:
6.17 [7'-déméthyl-7'-i.propyl-dihydro-MeBmt]^1-Ciclosporine;
6.18 [7'-déméthyl-7'-éthyl-dihydro-MeBmt]^1-[Val]^2-Ciclosporine;
6.19 [7'-déméthyl-7'-éthyl-dihydro-MeBmt]^1-[Nva]^2-Ciclosporine;
6.20 [7'-déméthyl-7'-phényl-dihydro-MeBmt]^1-[Val]^2-Ciclosporine;
6.21 [7'-déméthyl-7'-éthyl-dihydro-MeBmt]^1-Ciclosporine.

5. Une composition pharmaceutique comprenant une cyclosporine telle que spécifiée à l'une quelconque des revendications 1 à 4, en association avec un diluant ou support pharmaceutiquement acceptables.

6. Une cyclosporine telle que spécifiée à l'une quelconque des revendications 1 à 4, pour l'utilisation comme médicament.

7. Utilisation d'une cyclosporine
(i) dans laquelle l'atome de carbone 3' du reste en position 1 ou l'atome de carbone β du reste en position 2 est substitué par un groupe O-acyle ou oxo, ou
(ii) dans laquelle l'atome de carbone 3' du reste en position 1 est substitué par un groupe C_{1-4}-alcoxyimino, dans laquelle le reste en position 2 est un reste (L)-isoleucyle, ou le reste en position 11 est un reste N-méthyl-(L)-alanyle, N-méthyl-(L)-isoleucyle ou N-méthyl-(L)-alloisoleucyle; ou
(iii)de formule XI telle qu'illustrée à la revendication 1 dans laquelle :
Z signifie -Val- ou -MeVal-:
lorsque
Z signifie -Val-,

* C L M S *

A signifie -MeBmt- ou -dihydro-MeBmt-; ou
lorsque
Z signifie -MeVal-
A signifie -3'-désoxy-MeBmt-, -3'-désoxy-dihydro-MeBmt-, -N-déméthyl-MeBmt-, -N-déméthyl-dihydro-MeBmt, -3'-désoxy-4'-déméthyl-dihydro-MeBmt- ou -MeLeu-: et
lorsque
Z signifie -Val-,
B signifie -αAbu- ou -Thr-;
lorsque
Z signifie -MeVal- et
A signifie -3'-désoxy-MeBmt-, -3'-désoxy-dihydro-MeBmt-, -3'-désoxy-4'-déméthyl-dihydro-MeBmt- ou -MeLeu-,
B signifie -αAbu-; ou
lorsque
Z signifie -MeVal- et
A signifie -N-déméthyl-MeBmt- ou -N-déméthyl-dihydro-MeBmt-,
B signifie -Thr-;
dans la préparation d'un médicament
pour améliorer ou augmenter l'efficacité d'une autre thérapie à un médicament chimiothérapeutique ou pour augmenter la sensibilité à ladite thérapie, ou pour réduire la dose chimiothérapeutique efficace d'une seconde substance médicamenteuse chimiothérapeutique, ou
comme adjuvant dans le traitement des états pathologiques caractérisés par une résistance à une seconde substance médicamenteuse chimiothérapeutique, ou pour augmenter ou améliorer le traitement chimiothérapeutique d'états pathologiques présentant ou caractérisés par une résistance audit traitement, ou pour inverser ou réduire la résistance d'un traitement chimiothérapeutique, ou pour restaurer la sensibilité à un traitement chimiothérapeutique, ou
comme adjuvant à une autre thérapie à un médicament chimiothérapeutique.

8. Une cyclosporine selon la revendication 7 qui est une cyclosporine telle que définie à l'un quelconque des points (i), (ii), (iv), (v) ou (vi) de la revendication 1 ou une cyclosporine telle que définie sous (iii) de la revendication 1 dans laquelle le reste en position 1 est 3'-O-acyl-substitué.

9. Une cyclosporine selon la revendication 7, choisie dans le groupe constitué par :
1.1 [3'-O-acétyl-MeBmt]^{1}-Ciclosporine;
1.4 [3'-O-acétyl-MeBmt]^{1}-[Nva]^{2}-Ciclosporine;
1.8 [3'-O-acétyl-MeBmt]^{1}-[(D)MeVal]^{11}-Ciclosporine:
1.9 [3'-O-acéty-MeBmt]^{1}-[Val]^{11}-Ciclosporine;
1.13 [3'-O-acétyl-MeBmt]^{1}-[O-acétyl-Thr]^{2}-Ciclosporine;
1.14 [3'-O-acétyl-N-déméthyl-MeBmt]^{1}-[O-acétyl-Thr]^{2}-Ciclosporine;
1.35 [O-acétyl-Thr]^{2}-Ciclosporine;
2.3 [MeAla]^{11}-Ciclosporine;
2.4 [Melle]^{11}-Ciclosporine;
2.5 [Meallolle]^{11}-Ciclosporine;
2.6 [MeLeu]^{11}-Ciclosporine;
3.1 [Val]^{11}-Ciclosporine;
3.2 [dihydro-MeBmt]^{1}-[Val]^{11}-Ciclosporine;
3.3 [3'-désoxy-MeBmt]^{1}-Ciclosporine;
3.4 [3'-désoxy-dihydro-MeBmt]^{1}-Ciclosporine;
3.5 [N-déméthyl-MeBmt]^{1}-[Thr]^{2}-Ciclosporine;
3.7 [Thr]^{2}-[Val]^{11}-Ciclosporine;
3.9 [3'-désoxy-4'-déméthyl-dihydro-MeBmt]^{1}-Ciclosporine;
et les cyclosporines individuelles 1.2 à 1.41, 2.1 et 2.2 et 3.6 à 3.10 de la revendication 4.

10. Une composition pharmaceutique comprenant une cyclosporine de structure telle que définie à l'une quelconque des revendications 7 à 9, en association avec un diluant ou véhicule pharmaceutiquement acceptables.

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11. Une cyclosporine dans laquelle le reste en position 1 est un reste -5'-des-(1-propényl)-5'-formyl-MeBmt-, sous forme libre ou sous forme 3'-O-protégée.

12. Une cyclosporine selon la revendication 11 choisie dans le groupe constitué par :
    5.1 la [3'-O-acétyl-5'-des-(1-propényl)-5'-formyl-MeBmt]^1-Ciclosporine;
    5.2 la [3'-O-acétyl-5'-des-(1-propényl()-5'-formyl-MeBmt]^1-[O-acétyl-Thr]^2-Ciclosporine;
    5.3 la [3'-O-acétyl-5'-des-(1-propényl)-5'-formyl-MeBmt]^1-[Val]^2-Ciclosporine; et
    5.4 la [3'-O-acétyl-5'-des-(1-propényl)-5'-formyl-MeBmt]^1-[Nva]^2-Ciclosporine.

13. Une cyclosporine dans laquelle le reste en position 1 est un reste [3'-désoxy-3'-oxo-MeBmt].

14. La [3'-désoxy-3'-oxo-MeBmt]^1-[Val]^2-Ciclosporine.

15. Une composition pharmaceutique comprenant le composé de la revendication 13, en association avec un diluant ou véhicule pharmaceutiquement acceptables.

16. Le composé de la revendication 14 pour l'utilisation comme médicament.