Title: COMPOUND FORMULATIONS OF 2-AMINO-1, 3-PROPYANEDIOL COMPOUNDS

Abstract: Pharmaceutical concentrate formulations comprising 2-amino-1,3-propanediol compounds, analogs thereof and salts thereof, particularly 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof in an organic solvent or semi-aqueous solvent and methods for administration of the undiluted and diluted concentrate are provided.
COMPOUND FORMULATIONS OF 2-AMINO-1,3-PROPANEDIOL COMPounds

Field of the Invention

This invention is concerned with pharmaceutical formulations of 2 amino-1,3-propanediol compounds, especially 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmacologically acceptable salt thereof, and analogs of these compounds. In particular, the invention is concerned with pharmaceutical formulations which are administrable parenterally, e.g., intravenously (i.v.).

Background of the Invention

2-amino-1,3-propanediol compounds, in particular, 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol (sometimes referred to as FTY720) as shown:

![Chemical structure](image)

2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol

and a pharmacologically acceptable salt thereof, are known to be useful as suppressants of rejection in organ or bone marrow transplantation or as therapeutic agents of various autoimmune diseases, as described, e.g., in EP 0627406B1.

While 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol, particularly its salt form, is soluble in water, crystalline deposits of this compound have been observed in aqueous solutions either shortly after preparation or upon storage. Addition of cyclodextrins to aqueous solutions of the compound as described in U.S. Patent No. 6,476,004, have been found to be effective in reducing crystalline deposits of the compound, however, use of cyclodextrins has been limited by cost and regulation. Crystalline deposits of the compound have also been observed in aqueous solutions containing sodium laurylsulfate or polyvinylpyrrolidone K12 PF as described in the afore-mentioned U.S. Patent 6,476,004.

A semi-aqueous formulation of the compound which contains ethanol and polyethylene glycol has been described in the afore-mentioned EP 0627406B1. While there
is no mention of the occurrence of crystalline deposits in this semi-aqueous formulation, the formulation exhibited problems such as local irritation and hemolysis upon i.v. injection due to the high concentration of ethanol and polyethylene glycol present in the formulation.

Accordingly, it still remains desirable, therefore, to develop physically stable pharmaceutical formulations of this compound and other 2-amino-1,3-propanediol compounds and pharmaceutically acceptable salts thereof, which are crystal-free upon storage, and such formulations are the subject matter of the present invention.

**Summary of the Invention**

The present invention provides pharmaceutical concentrate formulations comprising 2-amino-1,3-propanediol compounds, analogs thereof and pharmaceutically acceptable salts thereof, particularly 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, which have improved stability, i.e., the formulations are free of crystals upon storage. The invention also provides pharmaceutical solutions of these compounds which are formed by the addition of a diluent vehicle to the concentrate formulation prior to administration.

**Detailed Description of the Invention**

All patent applications and patents cited herein are hereby incorporated by reference in their entirety.

The present invention relates to pharmaceutical organic concentrate formulations comprising 2-amino-1,3-propanediol compounds and salts thereof, particularly 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, and analogs of these compounds, in an organic solvent comprising ethanol and/or propylene glycol, and pharmaceutical semi-aqueous concentrate formulations comprising the aforementioned compounds in a semi-aqueous solvent comprising ethanol and propylene glycol. The concentrate formulations are free of crystals when stored at ambient and refrigerated conditions for extended periods of time, e.g., more than six months. The present invention also relates to pharmaceutical solutions which are formed by the addition of a diluent vehicle to the concentrate formulations prior to administration. The pharmaceutical solutions when administered parenterally are non-hemolytic, non-foaming and non-irritating.
Examples of the afore-mentioned compounds useful in the pharmaceutical concentrate formulations and pharmaceutical solutions of the present invention are compounds as disclosed in EP627406B1, e.g. a compound of formula I

\[
\begin{align*}
&\text{CH}_2\text{OR}_3 \\
&R_4 R_5 N - \text{CH}_2\text{OR}_2 \\
&R_1
\end{align*}
\]

wherein \(R_1\) is a straight- or branched \((C_{12-22})\)chain
- which may have in the chain a bond or a hetero atom selected from a double bond, a triple bond, O, S, NR, wherein \(R_6\) is H, alkyl, aralkyl, acyl or alkoxycarbonyl, and carbonyl, and/or
  - which may have as a substituent alkoxy, alkenyloxy, alkynylloxy, aralkyloxy, acyl, alkylamino, alkythio, acylylamino, alkoxycarbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

\(R_1\) is
- a phenylalkyl wherein alkyl is a straight- or branched \((C_{6-20})\)carbon chain; or
- a phenylalkyl wherein alkyl is a straight- or branched \((C_{1-32})\)carbon chain wherein said phenylalkyl is substituted by
  - a straight- or branched \((C_{6-20})\)carbon chain optionally substituted by halogen,
  - a straight- or branched \((C_{6-20})\)alkoxy chain optionally substituted by halogen,
  - a straight- or branched \((C_{6-20})\)alkenyloxy,
  - phenylalkoxy, halophenylalkoxy, phenylalkoxyalkyl, phenoxyalkoxy or phenoxyalkyl,
  - cycloalkylalkyl substituted by \(C_{6-20}\)alkyl,
  - heteroaryalkyl substituted by \(C_{6-22}\)alkyl,
  - heterocyclic \(C_{2-20}\)alkyl or
  - heterocyclic alkyl substituted by \(C_{2-20}\)alkyl,

and wherein the alkyl moiety may have
- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR, wherein \(R_4\) is as defined above, and
- as a substituent alkoxy, alkenyloxy, alkynylloxy, aralkyloxy, acyl, alkylamino, alkythio, acylylamino, alkoxycarbonyl, alkoxy carbonylamino, acyloxy, alkyl carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and

each of \(R_2, R_3, R_4\) and \(R_5\), independently, is H, \(C_{1-4}\) alkyl or acyl
or a pharmaceutically acceptable salt thereof;
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II

```
CH₂OR'
R'R'N-C-(CH₂)₂-
R'R'
CH₂OR'
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wherein m is 1 to 9 and each of R'_2, R'_3, R'_4 and R'_5, independently, is H, alkyl or acyl, or a pharmaceutically acceptable salt thereof;

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

```
W-C-Z₂-
\begin{array}{c}
\text{NR''₁,R''₂} \\
\text{(CH₂)m,OR''₃}
\end{array}
```

wherein W is H; C₅₆alkyl, C₂₆alkenyl or C₂₆alkynyl; unsubstituted or by OH substituted phenyl; R''₄O(CH₂)n; or C₁₆alkyl substituted by 1 to 3 substituents selected from the group consisting of halogen, C₃₋₆cycloalkyl, phenyl and phenyl substituted by OH;

X is H or unsubstituted or substituted straight chain alkyl having a number p of carbon atoms or unsubstituted or substituted straight chain alkoxy having a number (p-1) of carbon atoms, e.g. substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆ alkyloxy, acyloxy, amino, C₁₋₆alkylamino, acylamino, oxo, haloC₁₋₆alkyl, halogen, unsubstituted phenyl and phenyl substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆alkyl, OH, haloC₁₋₆alkylamino, acylamino, haloC₁₋₆alkyl and halogen; Y is H, C₁₋₆alkyl, OH, C₁₋₆alkoxy, acyl, acyloxy, amino, C₁₋₆alkylamino, acylamino, haloC₁₋₆alkyl and halogen; Z₂ is a single bond or a straight chain alkylene having a number or carbon atoms of q,

each of p and q, independently, is an integer of 1 to 20, with the proviso of 6≤p+q≤23, m' is 1, 2 or 3, n is 2 or 3,
each of R''₁, R''₂, R''₃ and R''₄, independently, is H, C₁₋₄alkyl or acyl, or a pharmaceutically acceptable salt thereof;

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

- 4 -
wherein $X_a$ is O, S, NR$_{1a}$ or a group $-(CH_2)_n=-, which group is unsubstituted or substituted by 1 to 4 halogen; n$_a$ is 1 or 2, R$_{1a}$ is H or (C$_{1-4}$)alkyl, which alkyl is unsubstituted or substituted by halogen; R$_{1b}$ is H, OH, (C$_{1-4}$)alkyl or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by 1 to 3 halogen; R$_{1b}$ is H, OH or (C$_{1-4}$)alkyl, wherein alkyl is unsubstituted or substituted by halogen; each R$_{2a}$ is independently selected from H or (C$_{1-4}$)alkyl, which alkyl is unsubstituted or substituted by halogen; R$_{3a}$ is H, OH, halogen or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by halogen; and R$_{3b}$ is H, OH, halogen, (C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by hydroxy, or O(C$_{1-4}$)alkyl wherein alkyl is unsubstituted or substituted by halogen; Y$_a$ is $-CH_2=, -C(O)=, -CH(OH)=, -C(=NOH)=, O$ or S, and R$_{4a}$ is (C$_{4-14}$)alkyl or (C$_{4-14}$)alkenyl;

or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in WO 02/076995, e.g. a compound of formula V

$$\text{R}_4\text{R}_3\text{N} \quad (\text{CH}_2)_{m_c}X_c\text{R}_2\text{c} \quad \text{V}$$

wherein

$m_c$ is 1, 2 or 3;

$X_c$ is O or a direct bond;

R$_{1c}$ is H; C$_{1-8}$ alkyl optionally substituted by OH, acyl, halogen, C$_{3-10}$cycloalkyl, phenyl or hydroxy-phenylene; C$_{2-6}$alkenyl; C$_{2-6}$alkynyl; or phenyl optionally substituted by OH;

R$_{2c}$ is
wherein $R_{6c}$ is H or C$_{1-4}$alkyl optionally substituted by 1, 2 or 3 halogen atoms, and $R_{6c}$ is H or C$_{1-4}$alkyl optionally substituted by halogen;

each of $R_{3c}$ and $R_{4c}$, independently, is H, C$_{1-4}$alkyl optionally substituted by halogen, or acyl, and

$R_c$ is C$_{13-20}$alkyl which may optionally have in the chain an oxygen atom and which may optionally be substituted by nitro, halogen, amino, hydroxy or carboxy; or a residue of formula (a)

![Chemical Structure (a)](image)

wherein $R_{7c}$ is H, C$_{1-4}$alkyl or C$_{1-4}$alkoxy, and $R_{8c}$ is substituted C$_{1-20}$alkanoyl, phenylC$_{1-4}$alkyl wherein the C$_{1-4}$alkyl is optionally substituted by halogen or OH, cycloalkylC$_{1-4}$alkoxy or phenylC$_{1-4}$alkoxy wherein the cycloalkyl or phenyl ring is optionally substituted by halogen, C$_{1-4}$alkyl and/or C$_{1-4}$alkoxy, phenylC$_{1-4}$alkoxy-C$_{1-4}$alkyl, phenoxyC$_{1-4}$alkoxy or phenoxyC$_{1-4}$alkyl,

$R_c$ being also a residue of formula (a) wherein $R_{8c}$ is C$_{1-14}$alkoxy when $R_{1c}$ is C$_{1-4}$alkyl, C$_{2-6}$alkenyl or C$_{2-6}$alkynyl,

or a compound of formula VI

![Chemical Structure (VI)](image)

wherein

$n_x$ is 2, 3 or 4

$R_{1x}$ is H, C$_{1-4}$alkyl optionally substituted by OH, acyl, halogen, cycloalkyl, phenyl or hydroxy-phenylene; C$_{2-6}$alkenyl; C$_{2-6}$alkynyl; or phenyl optionally substituted by OH;

$R_{2x}$ is H, C$_{1-4}$alkyl or acyl

each of $R_{3x}$ and $R_{4x}$, independently is H, C$_{1-4}$alkyl optionally substituted by halogen or acyl,

$R_{5x}$ is H, C$_{1-4}$alkyl or C$_{1-4}$alkoxy, and

$R_{6x}$ is C$_{1-20}$alkanoyl substituted by cycloalkyl; cycloalkylC$_{1-4}$alkoxy wherein the cycloalkyl ring is optionally substituted by halogen, C$_{1-4}$alkyl and/or C$_{1-4}$alkoxy; phenylC$_{1-4}$alkoxy
wherein the phenyl ring is optionally substituted by halogen, C_{1-4}alkyl and/or C_{1-4}alkoxy,
R_{6x} being also C_{1-14}alkoxy when R_{1x} is C_{2-6}alkyl substituted by OH, or pentyloxy or hexyloxy when R_{1x} is C_{1-4}alkyl,
provided that R_{6x} is other than phenyl-butylenoxy when either R_{6x} is H or R_{1x} is methyl, or a pharmaceutically acceptable salt thereof;
- Compounds as disclosed in WO02/06268AI, e.g., a compound of formula VII

\[ \begin{align*}
R_{3d} & \quad \text{OR}_{9d} \\
R_{4d} & \quad \text{OR}_{9d} \\
R_{5d} & \quad \text{OR}_{9d} \\
R_{6d} & \quad \text{OR}_{9d} \\
R_{7d} & \quad \text{OR}_{9d} \\
R_{8d} & \quad \text{OR}_{9d} \\
R_{9d} & \quad \text{OR}_{9d} \\
\text{NR}_{1d} & \quad \text{R}_{2d} \\
\text{(CH}_2)_n \text{S} & \quad \text{X}_d \\
\text{Y}_d & \quad \text{R}_{6d}
\end{align*} \]

wherein each of R_{1d} and R_{2d}, independently, is H or an amino-protecting group;
R_{3d} is hydrogen, a hydroxy-protecting group or a residue of formula
\[ \quad \text{P} \quad \text{OR}_{9d} \quad \text{OR}_{9d} \]

R_{4d} is lower alkyl;
n_{4d} is an integer of 1 to 6;
X_{4d} is ethylene, vinylene, ethynylene, a group having a formula – D-CH₂⁻ (wherein D is carbonyl, – CH(OH)⁻, O, S or N), aryl or aryl substituted by up to three substituents selected from group a as defined hereinafter;
Y_{4d} is single bond, C_{1-10}alkylenes, C_{1-10}alkylenes which is substituted by up to three substituents selected from groups a and b, C_{1-10}alkylenes having O or S in the middle or end of the carbon chain, or C_{1-10}alkylenes having O or S in the middle or end of the carbon chain which is substituted by up to three substituents selected from groups a and b;
R_{5d} is hydrogen, cycloalkyl, aryl, heterocycle, cycloalkyl substituted by up to three substituents selected from groups a and b, aryl substituted by up to three substituents selected from groups a and b, or heterocycle substituted by up to three substituents selected from groups a and b;
each of R_{6d} and R_{7d}, independently, is H or a substituent selected from group a;
each of R_{8d} and R_{9d}, independently, is H or C_{1-4}alkyl optionally substituted by halogen;
<group a> is halogen, lower alkyl, halogeno lower alkyl, lower alkoxy, lower alkoxy, lower alkylthio, carboxyl, lower alkoxycarboxyl, hydroxy, lower aliphatic acyl, amino, mono-lower alkenamino, di-lower alkenamino, lower aliphatic acylamino, cyano or nitro; and

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<group b> is cycloalkyl, aryl, heterocycle, each being optionally substituted by up to three substituents selected from group a;
with the proviso that when R_{5d} is hydrogen, Y_{e} is a either a single bond or linear C_{1-10} alkyne, or a pharmacologically acceptable salt or ester thereof;

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

\[
\text{(CH}_2\text{n)}_{6} \text{X}\text{Y}\text{R}_{6d} \text{R}_{5e}
\]

wherein R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, n_{e}, X_{e} and Y_{e} are as disclosed in JP-14316985; or a pharmacologically acceptable salt or ester thereof;

- Compounds as disclosed in WO 03/29184 and WO 03/29205, e.g. compounds of formula IX

\[
\text{NH}_{2} \text{CH}_{2}\text{OR}_{4f} \text{CH}_{3}\text{OR}_{5f}
\]

wherein X_{f} is O or S, and R_{1f}, R_{2f}, R_{3f} and n_{f} are as disclosed in WO 03/29184 and WO 03/29205, each of R_{4f} and R_{5f}, independently is H or a residue of formula

\[
\text{OR}_{4f} \text{OR}_{5f}
\]

wherein each of R_{4f} and R_{5f}, independently, is H or C_{1-alkyl} optionally substituted by halogen; e.g. 2-amino-2-[4-(3-benzoyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(benzoyloxyphenylthio)-2- chlorophenyl]propyl-1,3-propane-diol, or a pharmacological salt thereof;

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

\[
\text{Ar} \text{R}_{1g} \text{R}_{2g} \text{R}_{3g} \text{(CH}_2\text{)}_{m} \text{R}_{4g}
\]

wherein

Ar is phenyl or naphthyl; each of m_{g} and n_{g} independently is 0 or 1; A is selected from COOH, PO_{2}H_{2}, PO_{2}H, SO_{2}H, PO(C_{1-3}alkyl)OH and 1H-tetrazol-5-yl; each of R_{1g} and R_{2g}
independently is H, halogen, OH, COOH or C\textsubscript{1-4}alkyl optionally substituted by halogen; R\textsubscript{3g} is H or C\textsubscript{1-4}alkyl optionally substituted by halogen or OH; each R\textsubscript{4g} independently is halogen, or optionally halogen substituted C\textsubscript{1-4}alkyl or C\textsubscript{1-3}alkoxy; and each of R\textsubscript{g} and M has one of the significances as indicated for B and C, respectively, in WO03/062252A1;

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

\[ \text{Ar}_{1h} - \text{R}_{2h} - \text{N} - \text{Ar}_{3h} - \text{(R}_{4h})_0 - \text{M} \]

wherein Ar is phenyl or naphthyl; n is 2,3 or 4; A is COOH, 1H-tetrazol-5-yl, PO\textsubscript{3}H\textsubscript{2}, PO\textsubscript{2}H\textsubscript{2}, -SO\textsubscript{3}H or PO(R\textsubscript{6h})OH wherein R\textsubscript{6h} is selected from C\textsubscript{1-4}alkyl, hydroxyC\textsubscript{1-4}alkyl, phenyl, -CO-C\textsubscript{1-3}alkoxy and -CH(OH)-phenyl wherein said phenyl or phenyl moiety is optionally substituted; each of R\textsubscript{1h} and R\textsubscript{2h} independently is H, halogen, OH, COOH, or optionally halogen substituted C\textsubscript{1-3}alkyl or phenyl; R\textsubscript{3h} is H or C\textsubscript{1-4}alkyl optionally substituted by halogen and/ or OH; each R\textsubscript{4h} independently is halogeno, OH, COOH, C\textsubscript{1-4}alkyl, S(O)\textsubscript{0.1 or 2}C\textsubscript{1-3}alkyl, C\textsubscript{1-3}alkoxy, C\textsubscript{3-6}cycloalkoxy, aroyl or aralkoxy, wherein the alkyl portions may optionally be substituted by 1-3 halogens; and each of R\textsubscript{g} and M has one of the significances as indicated for B and C, respectively, in WO03/062248A2.

When the compounds of formula I to XI have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof are embraced. Compounds of formula III or IVb, when the carbon atom bearing the amino group is asymmetric, have preferably the R-configuration at this carbon atom.

The compounds of formula I to XI may exist in free or salt form. Examples of pharmaceutically acceptable salts of the compounds of the formula I to XI include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, or, when appropriate, salts with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. The compounds and salts of the combination of the present invention encompass hydrate and solvate forms.
Acyl as indicated above may be a residue $R'_y\text{-CO-}$ wherein $R'_y$ is C$_{1\text{st}}$alkyl, C$_3$-cycloalkyl, phenyl or phenyl-C$_{1\text{st}}$alkyl. Unless otherwise stated, alkyl, alkoxy, alkenyl or alkynyl may be straight or branched.

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

Preferred compounds of formula I are those wherein $R_1$ is C$_{13-20}$alkyl, optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably those wherein $R_1$ is phenylalkyl substituted by C$_{6-14}$alkyl chain optionally substituted by halogen and the alkyl moiety is a C$_{1-9}$alkyl optionally substituted by hydroxy. More preferably, $R_1$ is phenyl-C$_{1-9}$alkyl substituted on the phenyl by a straight or branched, preferably straight, C$_{6-14}$alkyl chain. The C$_{6-14}$alkyl chain may be in ortho, meta or para, preferably in para.

Preferably each of $R_3$ to $R_5$ is H.

A preferred compound of formula I is 2-amino-2-tetradecyl-1,3-propanediol. A particularly preferred compound of formula I is FTY720, i.e. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form, e.g. the hydrochloride, as shown:

![Structure of FTY720](image)

A preferred compound of formula II is the one wherein each of $R'_2$ to $R'_5$ is H and m is 4, i.e. 2-amino-2-[2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl]propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound A), e.g. the hydrochloride.

A preferred compound of formula III is the one wherein W is CH$_3$, each of $R''_1$ to $R''_3$ is H, $Z_2$ is ethylene, X is heptyloxy and Y is H, i.e. 2-amino-4-(4-heptyloxyphenyl)-2-methylbutanol, in free form or in pharmaceutically acceptable salt form (referred to hereinafter as Compound B), e.g. the hydrochloride. The R-enantiomer is particularly preferred.
A preferred compound of formula IVa is the FTY720-phosphate (R_{2a} is H, R_{3a} is OH, X_{a} is O, R_{1a} and R_{1b} are OH). A preferred compound of formula IVb is the Compound B-phosphate (R_{2a} is H, R_{3b} is OH, X_{a} is O, R_{1a} and R_{1b} are OH, Y_{a} is O and R_{4a} is heptyl). A preferred compound of formula V is Compound A-phosphate.

A preferred compound of formula V is phosphoric acid mono-[(R)-2-amino-2-methyl-4-(4-pentyloxy-phenyl)-butyl]ester.

A preferred compound of formula VIII is (2R)-2-amino-4-[3-(4-cyclohexyloxybutyl)]-benzo[b]thien-6-yl]-2-methylbutan-1-ol.

In one aspect, a pharmaceutical organic concentrate formulation (hereinafter referred to as organic concentrate) is provided which comprises one of the afore-mentioned compounds, preferably 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, in an organic solvent comprising 0-78.9 % (w/v) of ethanol (using a density value for ethanol of 0.789 gm/cm³) in propylene glycol. In a preferred embodiment, the organic solvent comprises 0-30 % (w/v) ethanol in propylene glycol. As an example, the organic solvent can comprise 20 % (w/v) ethanol in propylene glycol. As another example, the organic solvent can comprise 100 parts by volume of propylene glycol.

The preferred compound, 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, can be prepared as described, e.g., in EP 0627406B1 and U.S. Patent No. 6,605,744. The preferred pharmaceutically acceptable salt of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol is hydrochloride. Examples of other pharmaceutically acceptable salts include, but are not limited to, hydrobromide, sulfate, acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate, benzenesulfonate, and the like.

The afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, are typically present in the organic solvent at a concentration of 0.01-10 mg/mL, preferably 0.1-5 mg/mL.

The organic concentrate can be prepared, e.g., by dissolving one of the afore-mentioned compounds or a pharmaceutically acceptable salt thereof in either ethanol or propylene glycol separately, or when these solvents are utilized in combination, first dissolving the compound or a pharmaceutically acceptable salt thereof in ethanol followed by the addition of propylene glycol. As another example, when utilizing ethanol and propylene glycol...
glycol in combination, the compound or a pharmaceutically acceptable salt thereof can be first dissolved in propylene glycol followed by the addition of ethanol. As another example, when utilizing ethanol and propylene glycol in combination, these two solvents can be mixed together followed by the addition of the compound or a pharmaceutically acceptable salt thereof. The organic concentrate can also include minor amounts of anti-oxidants, surfactants, buffers, preservatives, solubilizers, complexing agents, stabilizers, chelating agents, etc.

The organic concentrates are stable, i.e., free of crystals, for an extended period of time, e.g. at least six months at temperatures of 5°C or 25°C, as indicated in standard tests utilized to observe crystals in solutions (see Experimental Example).

The organic concentrates can be utilized as is in various topical or oral applications or other routes, or can be diluted prior to administration. Accordingly, in another aspect, a pharmaceutical solution is provided which comprises an organic concentrate as described above and a diluent vehicle.

The type of diluent vehicle selected for admixture with the organic concentrate will depend on the route of administration and in particular on whether the compound, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol, is present in the organic concentrate in base or salt form. When the compound is in its salt form, the diluent vehicle typically comprises water or an isotonic solution such as a dextrose solution or a mannitol solution. When the compound is present as a free base, the diluent vehicle comprises an acidification agent, i.e., an inorganic or organic acid. Addition of an acidification agent to the organic concentrate containing the base form of the compound, prevents the base from precipitating out of the organic concentrate upon dilution with a water-based dilution vehicle by converting the base to a pharmaceutically acceptable salt. Examples of inorganic acids are hydrochloric acid, hydrobromic acid, sulfuric acid and the like. Examples of organic acids are acetic acid, fumaric acid, maleic acid, benzoic acid, citric acid, malic acid, methanesulfonic acid, benzenesulfonic acid, etc. The diluent vehicle utilized in admixture with the organic concentrate containing the base form of the compound can further comprise water, an isotonic solution, one or more solubilizers, e.g., surfactants, cyclodextrins and derivatives thereof, crystal inhibitors or combinations thereof.

The organic concentrate and diluent vehicle can be prepared and stored separately, e.g., as a pharmaceutical kit. Prior to administration the organic concentrate and diluent
vehicle can be combined to form a pharmaceutical solution. The pharmaceutical solution so formed may be preferably used immediately or within a short time of being formed, e.g., within 24 hours. Alternatively, the organic concentrate and a predetermined amount of diluent, may be loaded each into separate chambers of a double-chamber vial system and only mixed immediately prior to administration, e.g., by i.v., to a patient.

The amount of diluent used in admixture with the organic concentrate to form a pharmaceutical solution may be chosen so as to obtain a desired concentration of one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, in the pharmaceutical solution. The amount of diluent used is also chosen so that the solution is stable long enough to be administered. As an example, the concentration of pharmaceutical solutions made from the organic concentrates are typically 0.006 to 0.06 mg/mL. Such pharmaceutical solutions are found to be stable for up to 24 hours.

The pharmaceutical solution comprising the pharmaceutically acceptable salt of the compound can be prepared, e.g., by mixing the organic concentrate with a diluent, such as water or an isotonic solution, e.g., a dextrose solution or a mannitol solution, in a suitable container. The pharmaceutical solution comprising the base form of the compound, can be prepared, e.g., by first acidifying the organic concentrate with an acid, e.g., hydrochloride, to convert the base into a salt, followed by the addition of solubilizers, water, an isotonic solution, crystal inhibitors or combinations thereof. The pharmaceutical solution can further comprise minor amounts of antioxidants, surfactants, solubilizers, complexing agents, stabilizers, chelating agents, buffering agents, preservatives, moisturizing agents, pH adjusting agents, isotonizing agents or combinations thereof.

A preferred pharmaceutical solution of a salt form of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol comprises 1 mL of 1 mg/mL organic concentrate diluted with 99 mL of 5% dextrose to yield a solution containing 0.01 mg/mL.

In another aspect, a pharmaceutical semi-aqueous concentrate formulation (hereinafter referred to as a semi-aqueous concentrate) is provided which comprises a pharmaceutically acceptable salt of one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol, in a semi-aqueous solvent comprising 40-83% (w/v) of an organic component (using a density of 0.8301 gm/cm³ for propylene glycol to ethanol, 1:9 weight ratio) in water, wherein the organic component contains 10-90 parts by
weight of ethanol and 10-90 parts by weight of propylene glycol having a combined total of 100. In a preferred embodiment, the semi-aqueous solvent comprises 50-70 % (w/v) of the organic component in water, wherein the organic component contains 10-30 parts by weight of ethanol and 70-90 parts by weight of propylene glycol. As an example, the semi-aqueous solvent comprises 50 % (w/v) of an organic component in water, wherein the organic component contains 20 parts by weight of ethanol and 80 parts by weight of propylene glycol.

The pharmaceutically acceptable salt of one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol, can be present in the semi-aqueous solvent at a concentration of 0.01-5 mg/mL, and preferably at a concentration of 0.1-0.5 mg/mL.

The semi-aqueous concentrate can be prepared, e.g., by mixing ethanol with propylene glycol, dissolving the pharmaceutically acceptable salt of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol in the ethanol/propylene mixture, followed by the addition of deionized water.

The semi-aqueous concentrate can be utilized as is for certain applications, e.g., oral or topical or other routes, or can be diluted prior to its administration. Accordingly, in another aspect, a pharmaceutical solution is provided which comprises the afore-mentioned semi-aqueous concentrate and a diluent vehicle. The diluent vehicle typically comprises water, an isotonic solution, e.g., a dextrose solution or a mannitol solution, one or more solubilizers, e.g., surfactants, cyclodextrins or derivatives thereof, crystal inhibitors or combinations thereof.

The amount of diluent used in admixture with the semi-aqueous concentrate to form a pharmaceutical solution may be chosen so as to obtain a desired concentration of a pharmaceutically acceptable salt thereof in the pharmaceutical solution. The amount of diluent used is also chosen so that the pharmaceutical solution is stable long enough to be administered. As an example, the concentration of the pharmaceutical solutions prepared from a semi-aqueous concentrate are typically 0.006 to 0.06 mg/mL. Such pharmaceutical solutions are found to be stable for up to 24 hours.

The pharmaceutical solution made up of a semi-aqueous concentrate containing a pharmaceutically acceptable salt of one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride, can be prepared, e.g., by mixing the
semi-aqueous concentrate with a diluent, such as water or an isotonic solution in a suitable container. The semi-aqueous pharmaceutical formulations can also include minor amounts of antioxidants, surfactants, solubilizers, complexing agents, stabilizers, chelating agents, buffering agents, preservatives, moisturizing agents, pH adjusting agents and isotonizing agents.

A preferred pharmaceutical solution of a salt form of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol comprises 3 mL of 0.3 mg/mL semi-aqueous concentrate diluted with 97 mL of 5% dextrose to yield a solution containing 0.01 mg/mL.

The semi-aqueous concentrate and diluent vehicle can be prepared and stored separately, e.g., as a pharmaceutical kit. Prior to administration the semi-aqueous concentrate and diluent vehicle can be combined to form a pharmaceutical solution. The pharmaceutical solution so formed may be preferably used immediately or within a short time of being formed, e.g., up to 24 hours. Alternatively, the semi-aqueous concentrate and a predetermined amount of diluent, may be loaded each into separate chambers of a double-chamber vial system and only mixed immediately prior to administration, e.g., by i.v., to a patient.

The organic and semi-aqueous concentrates and their respective pharmaceutical solutions as described above can be administered by conventional routes such as oral, topical and parenteral, e.g., by infusion or injection. In a preferred embodiment, the pharmaceutical solutions prepared from either the organic concentrate or semi-aqueous concentrate, are administered parenterally as an infusion solution.

Accordingly, in one embodiment, a method is provided for administering one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, for the treatment of a disease sensitive to treatment with the compound or a pharmaceutically acceptable salt thereof to a patient in need of such treatment, the method comprising administering the organic concentrate or semi-aqueous concentrate to the patient.

In another embodiment, a method is provided for administering one of the afore-mentioned compounds, e.g., 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, for the treatment of a disease sensitive to treatment with the compound or a pharmaceutically acceptable salt thereof to a patient in need of such treatment, the method comprising:
(a) diluting the organic concentrate or semi-aqueous concentrate with a diluent vehicle to form a pharmaceutical solution; and

(b) administering the pharmaceutical solution to the patient.

The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention can be used for the suppression of rejection after organ or bone marrow transplantation, immunosuppressive sustentation therapy, treatment of eye diseases such as Behcet's disease and uveitis, and dermatitis inclusive of psoriasis, atopic dermatitis, contact dermatitis and allergic dermatitis. In particular, the concentrates and pharmaceutical solutions can be used for the prophylaxis and treatment of various applicable diseases (e.g., immunosuppressant for organ or bone marrow transplantation, various autoimmune diseases, various allergic diseases and the like).

The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention can be used, in the treatment and prophylaxis of resistance or rejection in organ or tissue transplantation (e.g., transplantation of heart, kidney, liver, lung, bone marrow, cornea, pancreas, small intestine, limb, muscle, nerves, fatty marrow, duodenum, skin and pancreatic islet cell, and xeno-transplantation), graft-versus-host (GvH) diseases by bone marrow or small intestine transplantation, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, nephrotic syndrome lupus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes mellitus, type II adult onset diabetes mellitus, uveitis, nephrotic syndrome, steroid-dependent and steroid-resistant nephrosis, palmoplantar pustulosis, allergic encephalomyelitis, glomerulonephritis, etc., and infectious diseases caused by pathogenic microorganisms.

The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention are also useful for treating inflammatory, proliferative and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses such as psoriasis, psoriatic arthritis, atopic eczema (atopic dermatitis), contact dermatitis and further eczematous dermatitises, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, acne, alopecia areata, eosinophilic fasciitis, and atherosclerosis. More particularly, the concentrates and pharmaceutical solutions of the present invention are useful in hair revitalizing, such as in the treatment of female or male pattern alopecia, or senile alopecia, by providing epilation prevention, hair germination,
and/or a promotion of hair generation and hair growth.

The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention are further useful in the treatment of respiratory diseases, for example, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, and reversible obstructive airways disease, including conditions such as asthma, including bronchial asthma, infantile asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, particularly chronic or inveterate asthma (e.g., late asthma and airway hyperresponsiveness), bronchitis and the like. The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention may be also useful for treating hepatic injury associated with ischemia. The concentrates and pharmaceutical solutions of the present invention are also applied to certain eye diseases such as conjunctivitis, keratoconjunctivitis, keratitis, vernal conjunctivitis, uveitis associated with Behcet's disease, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, keratoleukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, severe intraocular inflammation and the like.

The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention are also useful for preventing or treating inflammation of mucosa or blood vessels (e.g., leukotriene B4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), necrotizing enterocolitis), or intestinal lesions associated with thermal burns. The organic and semi-aqueous concentrates and pharmaceutical solutions of the present invention are further useful for treating or preventing renal diseases including interstitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome and diabetic nephropathy; nervous diseases selected from multiple myelitis, Guillain-Barre syndrome, Meniere's disease and radiculopathy; endocrine diseases including hyperthyroidism and Basedow's disease; hematologic diseases including pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia; bone diseases including osteoporosis; respiratory diseases including sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; skin diseases including dermatomyositis, vitiligo vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases including arteriosclerosis, aortitis, polyarteritis nodos and amyocardiosis; collagen disease including sclerosis, Wegener's granuloma and Sjogren's syndrome; adiposis;
eosinophilic fasciitis; periodontal disease; nephrotic syndrome; hemolytic uremic syndrome; and muscular dystrophy.

Further, the concentrates and pharmaceutical solutions of the present invention are indicated in the prophylaxis and treatment of diseases including intestinal inflammations or allergies such as Coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease or ulcerative colitis; and food related allergic diseases which have symptomatic manifestation remote from the gastrointestinal tract, for example, migraine, rhinitis and eczema.

Generally, the organic concentrate, the semi-aqueous concentrate, and pharmaceutical solutions made therefrom, may be administered in an amount which is therapeutically effective against a disease or condition which can be treated by administration of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof, or one of the other disclosed compounds. The exact amount of 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or pharmaceutically acceptable salt thereof or other disclosed compound to administer can vary widely. However, the dose administered to an animal, particularly a human should be sufficient to effect a therapeutic response. The dose may depend on the particular compound, route of administration, the rate of administration, the strength of the particular concentrate or pharmaceutical solution employed, the nature of the disease or condition being treated, and the sex, age and body weight of the patient. The size of the dose may also depend on the existence, nature and extent of any adverse side-effects that may accompany the administration of the concentrate or pharmaceutical formulation.

The organic and semi-aqueous concentrates and their respective pharmaceutical solutions can be used in combination with other immunosuppressant(s), steroid(s) (e.g., prednisolone, methylprednisolone, dexamethasone, hydrocortisone and the like) or nonsteroidal antiinflammatory agent. The administration of a combination of active agents may be simultaneous or consecutive, with either one of the active agents being administered first. The dosage of the active agents of a combination treatment may depend on effectiveness and site of action of each active agent, as well as synergistic effects between the agents used for combination therapy.
The present invention is described in more detail by referring to Examples and Comparative Examples. In the examples, the present compound refers to 2-amino-2-[2-(4-octylophenyl)ethyl]-propane-1,3-diol hydrochloride.

Example 1

1.0 mg/mL of the present compound in 20/80 (v/v) ethanol/propylene glycol

100 mg of the present compound is dissolved in 20 g of ethanol followed by the addition of propylene glycol to qs. 100 mL.

Example 2

1.0 mg/mL of the present compound in 100% propylene glycol

100 mg of the present compound is dissolved in 100 mL propylene glycol.

Example 3

0.3 mg/mL of the present compound in 10/40 (v/v) ethanol/propylene glycol in water

10 g of ethanol are mixed with 40 g of propylene glycol, followed by dissolving 0.3 mg of the present compound in the ethanol/propylene glycol mixture. Subsequent, deionized water or water for injection (WFI) is added to qs. 100 mL.

Comparative Example 1

0.1-10 mg/mL of the present compound in water

0.1-10 mg of the present compound is dissolved in 100 mL of deionized water.

Comparative Example 2

0.2 mg/mL of the present compound in 5% ethanol in water

0.2 mg of the present compound is dissolved 5 g of ethanol, followed by the addition of deionized water to qs. 100 mL.

Experimental Example

Physical stability
Solution clarity of Examples 1-3 and Comparative Examples 1 and 2 is monitored by manual inspection hood and microscopy. Formulations are stored in 25°C and 5°C chambers. The samplings are performed at two weeks, one, three and six months time points. At the pre-determined time, samples are pulled and examined for clarity and the absence of crystals as described below.

The clarity of the solution samples are primarily checked by the manual particulate inspection hood (M.W. Technologies Inc.). Each sample (in a clear vial) is placed against black background under Tyndal light. The vial is gently swirled in a circular motion. Sub-visible crystals are easily observed as they move and reflect the light.

The microscopic method is performed to confirm the shape and size of the crystals. The solution is sampled and dropped onto a clean glass slide and the presence or absence of crystals is observed under the microscope.

Utilizing the manual particulate inspection hood and microscopic methods, all the samples taken from solutions prepared in Examples 1-3 are observed to be clear with no visible crystals. Samples taken from solutions prepared in Comparative Examples 1 and 2 are hazy and found to contain crystals.
We Claim:

1. A pharmaceutical organic concentrate formulation comprising a 2-amino-1,3-propanediol compound, an analog thereof or a pharmaceutically acceptable salt thereof, in an organic solvent comprising 0-78.9% (w/v) of ethanol in propylene glycol.

2. The organic concentrate formulation of Claim 1, wherein the compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof.

3. The organic concentrate formulation of Claim 1, wherein the organic solvent comprises 0-30% (w/v) ethanol in propylene glycol.

4. The organic concentrate formulation of Claim 3, wherein the organic solvent comprises 20% (w/v) ethanol in propylene glycol.

5. The organic concentrate formulation of Claim 1, wherein the organic solvent comprises 100 parts by volume of propylene glycol.

6. The organic concentrate formulation of Claim 1, wherein the compound, analog or salt thereof is at a concentration of 0.01-10 mg/mL.

7. The organic concentrate organic formulation of Claim 6, wherein the compound, analog or salt thereof is at a concentration of 0.1-5 mg/mL.

8. A pharmaceutical solution comprising a pharmaceutical organic concentrate formulation according to Claim 1 and a diluent vehicle.

9. The pharmaceutical solution of Claim 8, wherein the diluent vehicle comprises an acidification agent.

10. The pharmaceutical solution of Claim 9, wherein the diluent vehicle further comprises water, an isotonic solution, a solubilizer, a crystal inhibitor or combinations thereof.

11. The pharmaceutical solution of Claim 8, wherein the concentrate formulation comprises 0.1-5 mg/mL of the compound or analog thereof in 0-30 % (w/v) of ethanol in propylene glycol, and wherein the diluent vehicle comprises an acidification agent, water, a solubilizer, crystal inhibitors or combinations thereof.
12. The pharmaceutical solution of Claim 8, wherein the concentrate formulation comprises 0.1-5 mg/mL of a pharmaceutically acceptable salt of the compound or analog thereof in 0-30 parts by weight of ethanol and 70-100 parts by weight of propylene glycol; and wherein the diluent vehicle comprises an isotonic solution.

13. A pharmaceutical kit comprising a concentrate formulation of Claim 1 and a diluent vehicle.

14. The pharmaceutical kit of Claim 13, wherein the concentrate formulation and diluent vehicle are in separate containers.

15. A method for preparing a pharmaceutical formulation for administration comprising:
   (a) preparing a solution of a 2-amino-1,3-propanediol compound, an analog thereof or a pharmaceutically acceptable salt thereof in an organic solvent comprising 0-78.9% (w/v) of ethanol in propylene glycol; and
   (b) diluting the solution prepared in (a) with a diluent vehicle.

16. The method of Claim 15, wherein the 2 amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof.

17. A method for preventing crystalline deposits of a 2-amino-1,3-propanediol compound, an analog thereof or a pharmaceutically acceptable salt thereof, the method comprising dissolving the 2-amino-1,3-propanediol compound, the analog or pharmaceutically acceptable salt thereof in an organic solvent comprising 0-78.9% (w/v) of ethanol in propylene glycol, in prophylaxis or treatment of suppression of rejection, autoimmune diseases or allergic diseases.

18. The method of Claim 17, wherein the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof.

19. A method for administering a 2-amino-1,3-propanediol compound, an analog thereof or a pharmaceutically acceptable salt thereof for the treatment of a disease sensitive to treatment with the 2-amino-1,3-propanediol compound, analog or salt thereof, to a patient in need of such treatment, the method comprising:
(a) diluting the concentrate formulation of Claim 1 with a diluent vehicle to form a pharmaceutical solution; and
(b) administering the pharmaceutical solution to the patient.

20. The method of Claim 19, wherein the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof.

21. The method of Claim 19, wherein in step (b) the pharmaceutical solution is administered parenterally.

22. A method for administering a 2-amino-1,3-propanediol compound, an analog thereof or a pharmaceutically acceptable salt thereof for the treatment of a disease sensitive to treatment with the 2-amino-1,3-propanediol compound, analog or salt thereof, to a patient in need of such treatment, the method comprising administering the concentrate formulation of Claim 1 to the patient.

23. The method of Claim 22, wherein the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical semi-aqueous concentrate formulation comprising a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof, in a semi-aqueous solvent comprising 40-83% (w/v) of an organic component in water, wherein the organic component contains 10-90 parts by weight of ethanol and 10-90 parts by weight of propylene glycol having a combined total of 100.

25. The semi-aqueous concentrate formulation of Claim 24, wherein the pharmaceutically acceptable salt of the 2-amino-1,3-propane diol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride.

26. The semi-aqueous concentrate formulation of Claim 24, wherein the semi-aqueous solvent comprises 50-70 % (w/v) of an organic component in water, and wherein the organic component contains 10-30 parts by weight of ethanol and 70-90 parts by weight of propylene glycol.
27. The semi-aqueous concentrate formulation of Claim 26, wherein the organic component contains 20 parts by weight of ethanol and 80 parts by weight of propylene glycol.

28. The semi-aqueous concentrate formulation of Claim 24, wherein the salt of the 2-amino-1,3-propanediol compound or analog thereof is at a concentration of 0.01-5 mg/mL.

29. The semi-aqueous concentrate formulation of Claim 28, wherein the salt of the 2-amino-1,3-propanediol compound or analog thereof is at a concentration of 0.1-0.5 mg/mL.

30. A pharmaceutical solution comprising the semi-aqueous concentrate formulation of Claim 24 and a diluent vehicle.

31. The pharmaceutical solution of Claim 30, wherein the semi-aqueous concentrate formulation comprises 0.1-5 mg/mL of a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof in a semi-aqueous solvent comprising 50-70% (w/v) of an organic component, wherein the organic component contains 10-30 parts by weight of ethanol and 70-100 parts by weight of propylene glycol.

32. A pharmaceutical kit comprising a concentrate formulation of Claim 24 and a diluent vehicle.

33. The pharmaceutical kit of Claim 32, wherein the concentrate formulation and diluent vehicle are in separate containers.

34. A method for preparing a pharmaceutical formulation for administration comprising:
   (a) preparing a solution of a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof in a semi-aqueous solvent comprising 40-83% (w/v) of an organic component in water, wherein the organic component contains 10-90 parts by weight of ethanol and 10-90 parts by weight of propylene glycol having a combined total of 100; and
   (b) diluting the solution prepared in step (a) with a diluent vehicle.

35. The method of Claim 34, wherein the pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride.
36. A method for preventing crystalline deposits of a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof, the method comprising dissolving the salt of the compound or analog thereof in a semi-aqueous solvent comprising 40-83% (w/v) of an organic component in water, wherein the organic component contains 10-90 parts by weight of ethanol and 10-90 parts by weight of propylene glycol having a combined total of 100, in prophylaxis or treatment of suppression of rejection, autoimmune diseases or allergic diseases.

37. The method of Claim 36, wherein the pharmaceutically acceptable salt of the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride.

38. A method for administering a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof for the treatment of a disease sensitive to treatment with the pharmaceutically acceptable salt of the 2-amino-1,3-propanediol compound or analog thereof, to a patient in need of such treatment, the method comprising:

(a) diluting the semi-aqueous concentrate formulation of Claim 24 with a diluent vehicle to form a pharmaceutical solution, and

(b) administering the pharmaceutical solution to the patient.

39. The method of Claim 38, wherein the pharmaceutically acceptable salt of the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride.

40. The method of Claim 38, wherein in step (b) the pharmaceutical solution is administered parenterally.

41. A method for administering a pharmaceutically acceptable salt of a 2-amino-1,3-propanediol compound or analog thereof for the treatment of a disease sensitive to treatment with a pharmaceutically acceptable salt of the compound or analog thereof to a patient in need of such treatment, the method comprising administering the semi-aqueous concentrate formulation of Claim 24 to the patient.
42. The method of Claim 41, wherein the pharmaceutically acceptable salt of the 2-amino-1,3-propanediol compound is 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol hydrochloride.
### A. CLASSIFICATION OF SUBJECT MATTER

| IPC    | A61K31/133 | A61K47/10 | A61P37/00 | A61P37/06 |

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

| IPC 7 | A61K | A61P |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 02/18395 A (MERCK &amp; CO., INC; MANDALA, SUZANNE; BERGSTROM, JAMES; HAJDU, RICHARD;) 7 March 2002 (2002-03-07) cited in the application page 18, lines 17-21</td>
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<td>1-42</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
  - **A** document defining the general state of the art which is not considered to be of particular relevance
  - **E** earlier document but published on or after the international filing date
  - **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - **O** document referring to an oral disclosure, use, exhibition or other means
  - **P** document published prior to the international filing date but later than the priority date claimed
  - **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - **Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - **Z** document member of the same patent family

Date of the actual completion of the international search:

17 October 2005

Date of mailing of the international search report:

04/11/2005

Name and mailing address of the ISA:

European Patent Office, P.B. 5018 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 940-2040, Tx. 31 651 epo nl, Fax (+31-70) 940-2016

Authorized officer:

Zimmer, B

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Form PCT/ISA/210 (second sheet) (January 2004)
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<td>X</td>
<td>EP 0 627 406 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD; YOSHITOMI PHARMACEUTICAL) 7 December 1994 (1994-12-07) page 240, lines 38-53</td>
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<td>A</td>
<td>EP 0 990 440 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD; MITSUBISHI PHARMA CORPORATION) 5 April 2000 (2000-04-05) abstract</td>
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<td>EP 1 050 301 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD; MITSUBISHI PHARMA CORPORATION) 8 November 2000 (2000-11-08) paragraph '0009'</td>
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<td>P,A</td>
<td>GB 2 400 318 A (* NOVARTIS AG; * MITSUBISHI PHARMA CORPORATION) 13 October 2004 (2004-10-13) page 1</td>
<td>1-42</td>
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</table>
INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 17-23 and 36-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Rule 39.1(iv) PCT—Method for treatment of the human or animal body by therapy

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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