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(54) **Title: PHARMACEUTICAL COMPOSITIONS**

(57) **Abrégé/Abstract:**

The present invention relates to pharmaceutical compositions of 2-Methyl- 41 - trifluoromethoxy-biphenyl-3-carboxylic acid [6-{cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]- amide, to the use of such compositions in therapeutic applications and to methods for manufacturing such compositions.

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(54) Title: TOPICAL PHARMACEUTICAL COMPOSITION INCLUDING REL-N- [6 - [(2R, 6S) - 2, 6 - DIMETHYL - 4 - MORPHOLINYL] -3 - PYRIDINYL] - 2 -METHYL -41 (TRIFLUOROMETHOXY) - [1,1' -BIPHENYL] - 3 - CARBOXAMIDE

(57) Abstract: The present invention relates to topical pharmaceutical compositions of 2 -Methyl - 41 - trifluoromethoxy-biphenyl - 3 - carboxylic acid [6 - (cis - 2, 6 - dimethyl -morpholin - 4 -yl) -pyridin - 3 -yl] - amide, to the use of such compositions in therapeutic applications and to methods for manufacturing such compositions.



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Pharmaceutical Compositions**Field of the invention**

5 The present invention relates to pharmaceutical compositions of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, to the use of such compositions in therapeutic applications and to methods for manufacturing such compositions. The invention further relates to a specific form of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-
10 pyridin-3-yl]-amide and to the manufacturing and use of such form.

Background of the invention

WO 2007/131201 and WO 2008/154259 disclose compounds with activity as hedgehog signalling pathway modulators, including 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic
15 acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide. Topical pharmaceutical compositions are not specifically disclosed.

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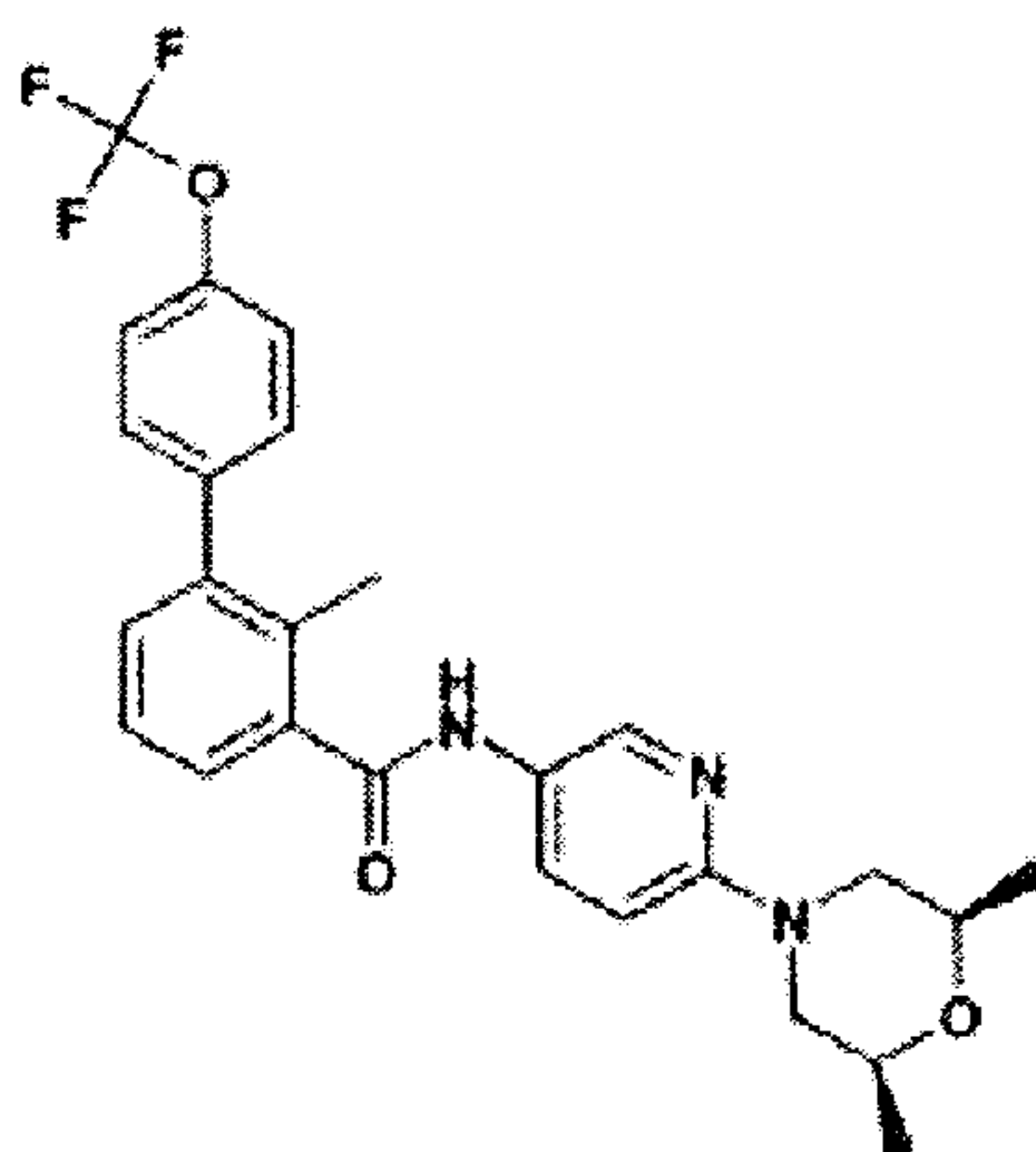
Summary of the invention

There is a need to provide a topical pharmaceutical composition comprising 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide which has advantageous properties such as optimum penetration of active compound
25 into the skin, limited systemic exposure, good stability and/or acceptance by the patient. Hence, it is a general object of the invention to provide compositions that possess such desirable properties, and these objectives are achieved by providing a composition as defined herein.

30 The invention provides in its broadest sense a topical pharmaceutical composition including the compound 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide:

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or a solvate thereof ("agent of the invention") and one or more excipients. The agent of the invention is also identified alternatively by the name: rel-N-[6-[(2R,6S)-2,6-dimethyl-4-morpholinyl]-3-pyridinyl]-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxamide or N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide. For the avoidance of doubt, the above mentioned chemical names all refer to the same chemical compound denoted by the above chemical structure and may be used interchangeably.

In an embodiment, the invention relates to a topical pharmaceutical composition comprising

- a) N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide;
- b) dimethylisorbide (DMI); and
- c) an oily phase.

Such compositions are preferably semi-solid. It was found by the present inventors that such compositions enable delivery of the agent of the invention into the skin in an efficient manner, they limit the systemic exposure by maintaining permeation through the skin at acceptable levels, they benefit from acceptance by the patient, and/or are stable.

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Further aspects of the invention are disclosed herein and include a solid form of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, methods of manufacturing and uses of these compositions. The compositions as described prove to be useful for the treatment of dermatological diseases as defined below.

Brief Description of the Drawings

- Fig 1 shows the human skin concentrations (penetration) of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide following application of compositions of the invention.
- 10 Fig 2 shows the levels of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide in de-epidermized pig skin 24 hrs after epicutaneous application of compositions of the invention.
- Fig 3 shows the powder X-ray diffraction pattern of 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide,
- 15 Form A.

Detailed Description of preferred embodiments

The invention may be more fully appreciated and objects other than those set forth above will
5 become apparent when consideration is given to the following description, including the
following glossary of terms and the concluding examples.

As used herein, "agent of the invention" means 2-Methyl-4'-trifluoromethoxy-biphenyl-3-
carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, and is intended to
10 represent amorphous and crystalline forms. "Agent of the invention" is intended to also
represent a solvate thereof or a prodrug thereof, a pharmaceutical acceptable salt thereof
and its mixtures. Preferably, the agent of the invention is 2-Methyl-4'-trifluoromethoxy-
biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide, present in
its free form, i.e. not as a salt.

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As used herein, the terms "including", "containing" and "comprising" are used herein in their
open, non-limiting sense. Where the plural form (e.g. compounds, excipients) is used, this
includes the singular (e.g. a single compound, a single excipient). "A compound" does not
exclude that (e.g. in a pharmaceutical composition) more than one compound (or a salt
20 thereof) is present.

It is further understood that the various embodiments, preferences and ranges of this
invention, as provided / disclosed in the specification and claims may be combined at will.
Further, depending on the specific embodiment, selected definitions, embodiments or ranges
25 may not apply. The following general definitions shall apply in this specification, unless
otherwise specified.

As used herein, the term "solvate" is used herein to describe a molecular complex
comprising the compound of the invention and one or more pharmaceutically acceptable
30 solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is
water.

As used herein, the term "agent of the invention" also includes co-crystals of 2-Methyl-4'-
trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-
35 amide, formed with suitable co-crystal formers. These co-crystals may be prepared by known
co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-
melting, or contacting in solution 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-
(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide with the co-crystal former under

crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163.

As used herein, the term "Prodrug" indicates a compound that may be converted under
5 physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, this term refers to a metabolic precursor of an agent of the invention that is pharmaceutical acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed in vivo to yield the parent compound of the invention, for
10 example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism. Prodrugs of a agent of the invention may be prepared by modifying functional groups present in the agent of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Prodrugs include compounds of the invention
15 wherein a hydroxyl group is bonded to any group that, when the prodrug of the agent of the invention is administered to a mammalian subject, cleaves to form a free hydroxy group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol groups in the agent of the invention. Suitable prodrugs include pharmaceutically acceptable esters of the agent of the invention. As used herein, the term
20 "pharmaceutically acceptable ester" refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6
25 carbon atoms, particularly formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid salts of the compounds of the invention. These salts can be prepared in situ during the final
30 isolation and purification of the compounds, or by separately reacting the base functions with a suitable organic or inorganic acid. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemi-sulfate,
35 heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methane-sulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluene-sulfonate, and undecanoate.

Also, basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others.

As used herein, the term "topical pharmaceutical composition" is known in the field (e.g. see European Pharmacopoeia, 6.3, 01/2009, 0132). Such compositions contain (i.e. include, comprise or consist of) i) the agent of the invention and ii) a matrix. The matrix (also referred to as "base") contains pharmaceutically acceptable excipients and is adapted to a topical application. Further, compositions of the invention may be formulated as gel, foam, tincture, (lip) stick, or spray. Consequently, viscosities of the compositions of the invention, may vary over a broad range, typically they are semi-solid or liquid, preferably semi-solid. Compositions of the invention are of the solution type, characterized in that the agent of the invention is dissolved in the matrix. In a preferred aspect the compositions are creams, having the benefit of greater patient acceptability.

According to one aspect, the invention provides a topical pharmaceutical composition including 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide and one or more pharmaceutically acceptable excipients.

In another embodiment, the invention provides a topical pharmaceutical composition including:

- a) the agent of the invention;
- b) one or more solvents;
- c) optionally an oily phase;
- d) optionally one or more antioxidants;
- e) optionally one or more consistency improvers
- f) optionally one or more surfactants;
- g) optionally one or more preservatives; and
- h) optionally one or more gelling agents.

In a further embodiment, the invention provides a topical pharmaceutical composition including:

- a) the agent of the invention;
- b) one or more solvents;
- c) an oily phase;
- d) optionally one or more antioxidants;

- e) optionally one or more consistency improvers
- f) optionally one or more surfactants;
- g) optionally one or more preservatives; and
- h) optionally one or more gelling agents

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In another embodiment, the invention provides a topical pharmaceutical composition including:

- a) the agent of the invention;
- b) dimethylisosorbide (DMI), propylene glycol and optionally one or more further sol-
10 vents;
- c) optionally an oily phase;
- d) optionally one or more antioxidants;
- e) optionally one or more consistency improvers;
- f) optionally one or more surfactants;
- 15 g) optionally one or more preservatives; and
- h) optionally one or more gelling agents.

In a further embodiment, the invention relates to a composition according to this aspect of the invention which contains one or more additional excipients. Suitable excipients may be
20 selected from the group consisting of antioxidants, gelling agents, ph adjusting agents / buffers, agents to modify consistency, preservatives, (co-)solvents, fillers, binders, disintegrators, flow conditioners, lubricants, fragrances, stabilizers, wetting agents, emulsifiers, solubilizers and salts for regulating osmotic pressure. Such excipients are known in the field, commercially available and may be identified in standard textbooks, such as the
25 Handbook of Pharmaceutical Excipients by R.C. Rowe et al. Such compositions are advantageous to specifically adapt to manufacturers or patients needs and thus improve product properties (like shelf life or patient compliance). Suitable excipients are explained below.

30 A solvent is an excipient which dissolves the agent of the invention. It is understood that one or more solvents may be used.

A preferred solvent in the compositions of the invention is dimethylisosorbide (DMI). In one embodiment, the solvent dimethylisosorbide (DMI) is present in the composition in a range of
35 from 5.0 to 15.0 wt%, preferably at from 7.0 to 13.0 wt%. In a particular embodiment DMI is present at 10.0 wt%.

In another embodiment, the composition further includes the solvent benzyl alcohol. Benzyl alcohol is preferably present in an amount of up to 10 wt%, more preferably in an amount of up to 5 wt%. In preferred embodiments, benzyl alcohol is present in the range of 0.5 to 5 wt%, e.g. in an amount of about 3 wt%.

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In another embodiment, the composition further includes the solvent diisopropyl adipate (DIPA). In one embodiment, DIPA is present in the composition in a range of from 10.0 to 20.0 wt%. Preferably, the total amount of DMI and DIPA is up to and including 30.0 wt%. More preferably, DIPA is present at from 12.0 to 18.0 wt% and most preferably DIPA is present at 15.0 wt%.

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In another embodiment of the invention, the composition includes the solvent propylene glycol. In one embodiment, propylene glycol is present in the composition at a range of from 0.5 to 20 wt%, and in particular at a range of from 1.0 to 3.0 wt%, more particularly 2.0%. In an alternative embodiment, propylene glycol is present at a range of from 7.0 to 13.0 wt%, particularly 10.0 wt%.

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In another embodiment of the invention, the composition includes at least one solvent selected from propylene glycol and DIPA.

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In another embodiment of the invention, the composition includes propylene glycol, DIPA or a mixture of propylene glycol and DIPA in a range of 10-35 wt%, preferably in the range of 15-30%, more preferably in the range of 17-25 wt% based on the weight of the composition.

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Preferably, according to the invention, the composition includes the solvent dimethylisobutide (DMI) and an additional solvent selected from: propylene glycol and DIPA. Preferred compositions may contain a mixture of DMI and propylene glycol; a mixture of DMI and DIPA; or a mixture of DMI, propylene glycol and DIPA, in each case optionally together with an additional solvent or solvents.

30

In another embodiment of the invention an oily phase is present, preferably comprising medium chain triglyceride (MCT). The oily phase is any phase which is not water soluble, and may include excipients such as medium chain triglycerides, paraffin, vaseline, polyalkylsiloxane, isopropylmyristate, isopropylpalmitate, isoadipate and vegetable oils/ olea herbaria, i.e. castor oil, olive oil. In one embodiment, the oily phase, such as MCT, is present at a range of from 2.0 wt% to 20 wt%. In another embodiment the oily phase is present at from 3.0 wt% to 18 wt%. In one particular aspect of the invention the oily phase is present at 5.0 wt%, and in an alternative is present at 15.0 wt%.

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It is understood that one or more antioxidants may be used. In one embodiment the antioxidant is present in the composition and is selected from the group consisting of phenole derivatives (e.g. butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA)); ascorbic acid derivatives (e.g. ascorbic acid, ascorbyl palmitate), tocopherol derivatives (e.g. Vitamin E, Vitamin E TPGS), bisulfite derivatives (Na bisulfite, Na meta bisulfite) and thio urea. In a particular embodiment the composition includes both butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). A suitable composition may contain up to 2 wt% antioxidant, preferably 0.05 – 0.5 wt%. In a particular embodiment, the composition includes from 0.05 to 0.15 wt% BHT and from 0.05 to 0.15 wt% BHA. Preferably, the composition includes 0.10 wt% BHT and 0.10 wt% BHA.

Agents to modify consistency, also named consistency improvers, are known in the field, and in another embodiment of the invention the composition includes such agents. It is understood that one or more of such agents may be used, e.g. cetyl alcohol, stearyl alcohol and mixtures thereof. A suitable composition may contain up to 15 wt%, for example from 5.0 to 10.0 wt% in total, of the consistency improver or improvers. In one embodiment, the composition includes the consistency improvers stearyl alcohol and cetyl alcohol. In another embodiment, the consistency improvers stearyl alcohol and cetyl alcohol are present in equal amounts. In one preferred embodiment, the composition includes stearyl alcohol in a range of from 2.0 to 6.0 wt% and cetyl alcohol in a range of from 2.0 to 6.0 wt%. In a particular embodiment, stearyl alcohol is present at 4 wt% and cetyl alcohol is present at 4 wt%.

Surfactants are surface active agents. It is understood that one or more surfactants may be used. In an embodiment of the invention, at least one surfactant is present in the composition. In one embodiment, the surfactant or surfactants are present in the range of from 0.5 to 6.0 wt%. In a particular embodiment, the surfactants glyceryl monostearate and sodium cetylstearyl sulfate (Lanette E®) are present in the composition. In one embodiment, glyceryl monostearate is present at from 1.0 wt% to 3.0 wt% and sodium cetylstearyl sulfate (Lanette E®) is present at from 0.1 to 2.0 wt%. In a particular embodiment of the invention, glyceryl monostearate is present at 2.0 wt% and sodium cetylstearyl sulfate (Lanette E®) is present at 1.0 wt%.

It is understood that one or more preservatives may be used. Preservatives are included in the pharmaceutical compositions of this invention to increase shelf life. In one embodiment at least one preservative is present in the composition and is selected from the group of acids (e.g. sorbic acid, benzoic acid); alcohols (e.g. benzyl alcohol), quaternary amines, phenols, and parahydroxybenzoates. In a preferred embodiment the preservative is benzyl alcohol. Benzyl alcohol may also act as a (co)-solvent in the compositions of the invention. In one

embodiment the preservative is present in the range of from 0.5 to 5.0 wt%. Preferably, benzyl alcohol is present at 3.0 wt%.

Gelling agents may optionally be included in the compositions of this invention to adjust
5 viscosity. It is understood that one or more gelling agents may be used. For example, gelling agents may be carbomers, acrylic acid derivatives or cellulose derivatives, such as hydroxypropylcellulose. A suitable composition may contain up to 5 wt% gelling agent. In one embodiment, the composition contains from 0.02 to 2.0 wt% gelling agent. In a preferred embodiment, the composition contains 0.5 wt% or 0.2 wt% gelling agent. Preferably, the
10 gelling agent is carbomer 974P.

Agents to adjust the pH or to provide a pH buffer are known in the field. It is understood that one or more of such agents may be used, such as sodium hydroxide. A suitable composition may contain such acids / bases to adjust the pH of the inventive composition in the range of
15 4 – 8, preferably 5 – 7, such as 6.5.

The amount of agent of the invention in the inventive composition may vary over a broad range, it is typically provided in an effective amount. An effective amount refers to an amount of the agent of the invention which, when administered to a mammal, particularly a human, is
20 sufficient to effect a treatment as defined below. Suitable amounts for the agent of the invention may be determined by the skilled person in routine experiments; typically they are in the range between 0.2 – 5 wt-%, preferably 0.5 – 2.0 wt-%, such as 0.25, 0.5, 0.75 or 1.0 wt% of the total composition.

25 The invention relates in another aspect to a method for manufacturing compositions as described herein comprising the steps of:

1. combining the lipophilic excipients as described herein to obtain a lipophilic phase, combining this phase with the agent of the invention, and melting the mixture.
2. combining the hydrophilic excipients and heating
- 30 3. combining the hydrophilic and lipophilic phases, then adjusting the pH.

A composition according to this invention may be prepared by processes that are known per se, but not yet applied for the present compositions where they thus form new processes. In general, the manufacture of a pharmaceutical composition comprises the step of combining
35 the agent of the invention with a matrix, e.g. by mixing, dissolving and/or lyophilizing. Such steps may also comprise heating or cooling the materials used. The agent of the invention is available according to known processes or according to processes as described herein; the

individual components of the matrix are either known per se or available according to known processes.

In one embodiment, the invention relates to a method of manufacturing a composition as described herein comprising the steps of

- combining all liquid non-aqueous excipients and the agent of the invention and optionally heating the mixture to 30 – 95°C to obtain a solution,
- melting the solid excipients at a temperature between 30 – 95°C to obtain a melt,
- combining the solution and melt, preferably at a temperature between 30 – 95 °C,
- optionally adding water or an aqueous phase to the combined mixture
- optionally cooling down the obtained composition.

The invention relates in another aspect to the use of such compositions as a pharmaceutical, particularly as a pharmaceutical for the use of dermatological diseases.

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Compositions comprising 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide are suitable for the treatment, including prophylaxis and delay of progression, of diseases related to modulation of activity of the hedgehog signaling pathway. In particular, the compositions herein are useful for the treatment of dermatological diseases. The term "dermatological diseases" as used herein includes all types of dermatological diseases, disorders or conditions in a mammal (in particular a human). In one particular embodiment of the invention, the compositions disclosed herein are useful to treat diseases or conditions including hyperproliferative skin conditions such as basal cell nevus syndrome (also called Gorlin's syndrome and/or nevoid basal cell carcinoma), a rare autosomal dominant genetic syndrome leading to cancers such as skin cancers, basal cell carcinoma (BCC), in particular superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma, sebaceous hyperplasia and psoriasis.

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Thus in one embodiment of the invention, the invention provides a composition as described herein for use in medicine. In another embodiment, the invention provides a composition for use in treating a dermatological disease, disorder or condition mediated by the hedgehog signaling pathway. In a further embodiment, the invention provides a composition for use in treating a hyperproliferative skin condition, or a dermatological disease, disorder or condition selected from Gorlin's syndrome, basal cell carcinoma, sebaceous hyperplasia and psoriasis.

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In another embodiment, the invention provides the use of a composition as described herein for the manufacture of a medicament for the treatment of a dermatological disease, disorder or condition mediated by the hedgehog signaling pathway. In a further embodiment, the

invention provides the use of a composition as described herein for the manufacture of a medicament for the treatment of a hyperproliferative skin condition, or a dermatological disease, disorder or condition selected from Gorlin's syndrome, basal cell carcinoma, sebaceous hyperplasia and psoriasis.

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In another embodiment, the invention relates to a method of treatment of a dermatological disease, disorder or condition mediated by the hedgehog signaling pathway (particularly selected from the group consisting of a hyperproliferative skin condition, or Gorlin's syndrome, basal cell carcinoma, sebaceous hyperplasia and psoriasis), which treatment
10 comprises administering to a subject in need of such treatment, particularly a human, an effective amount of a composition as described herein.

In a further embodiment, the invention relates to a method as described herein, wherein a composition as described herein is administered in combination with another pharmaceutical-
15 ly acceptable composition, either simultaneously or in sequence.

For treatment using a composition of the invention, the appropriate dosage will, of course, vary depending upon, for example, the type of composition used, the individual host and the nature and severity of the conditions being treated. However, in general, for satisfactory
20 results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.01 g to about 1.0 g, of a compound of the present invention, conveniently administered, for example, in divided doses up to four times a day.

The invention relates in another aspect to specific forms of the agent of the invention.

25

In one embodiment, the invention relates to 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide in crystalline form.

Particularly, the invention relates to the polymorphic form A as defined herein, substantially
30 free of other polymorphic forms of the agent of the invention. In a further embodiment, the invention relates to 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide form A comprising the following X-ray powder diffraction peaks: 2-theta values 12.9, 16.5, 17.0, 18.6, 19.9, 21.2, 22.4, 24.3, 25.8 and 26.1. Form A is produced following the synthetic methods described herein.

35

The invention further relates to the polymorphic form B as defined herein, either substantially free of other polymorphic forms of the agent of the invention or in a mixture with other

polymorphic forms of the agent of the invention. Form B is produced following the synthetic methods described herein.

The invention further relates to the amorphous form of the agent of the invention as described herein.

5

Fig 3 shows the powder X-ray diffraction pattern of polymorph A. Relative intensities are dependent on several factors including particle size, shape and method of sample preparation, thus are subject to variation. The data was obtained using the instrument Scintag INC, irradiation CuK α (45 kV, 40mA), continuous scan, scan rate 0.5°/min (2 theta value), scan range 1.5° - 40° (2 theta value).

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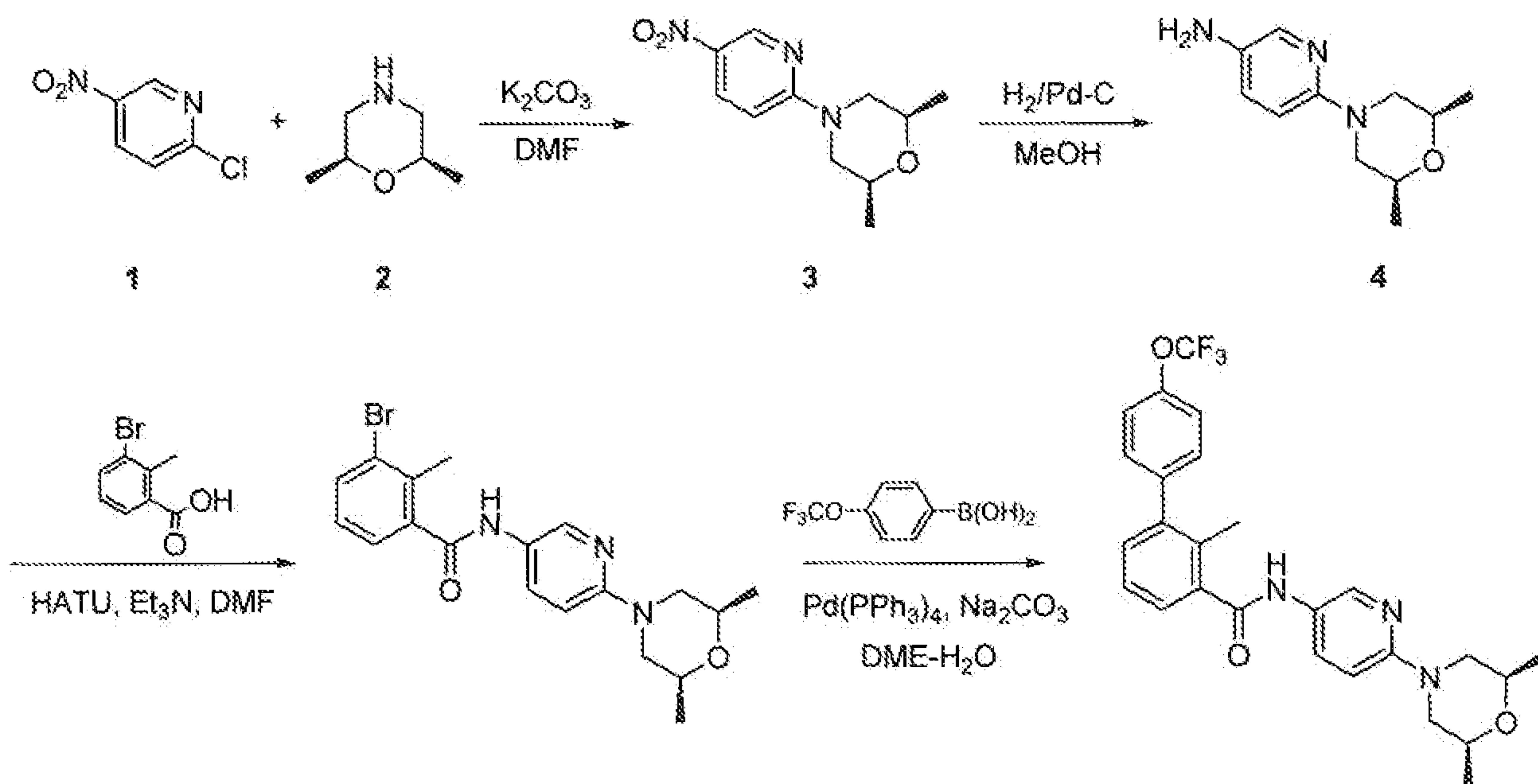
In a further embodiment, the invention relates to the agent of the invention obtainable by or obtained by a process as described herein.

15 Modes for carrying out the invention

The following Examples serve to illustrate the invention without limiting the scope thereof. It is understood that the invention is not limited to the embodiments set forth herein, but embraces all such forms thereof as come within the scope of the disclosure.

20

A. Synthesis of N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide:



5

25 Step 1: To a solution of 2-chloro-5-nitropyridine 1 (5.58 g, 35.2 mmol) and *cis*-2,6-

dimethylmorpholine (4.05 g, 35.2 mmol) in anhydrous DMF (30 mL) was added K_2CO_3 (9.71 g, 70.4 mmol). The mixture was heated at 50°C overnight. After concentration, the residue is partitioned between EtOAc and water. The EtOAc layer is dried over anhydrous Na_2SO_4 and concentrated to give crude product **3** as a yellow solid, after purification by silica gel chromatography, obtained pure product (7.80 g, 93.2%). LC-MS *m/z*: 238.2 (M+1).

Step 2: The above material **3** (7.30g, 30.8 mmol) was hydrogenated in the presence of 10% Pd-C (1.0 g) in MeOH (120 mL) under hydrogen overnight. The suspension was filtered through celite and the filtrate was concentrated to give the crude product **4** (5.92 g) as a dark brown oil which was used directly in the next step without further purification. LC-MS *m/z*: 208.2 (M+1).

Step 3: To a solution of 3-bromo-2-methyl benzoic acid (2.71 g, 12.6 mmol), 6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-amine **4** (2.61 g, 12.6 mmol), and HATU (4.80 g, 12.6 mmol) in anhydrous DMF (30 mL) was added diisopropylethylamine (6.58 mL, 37.8 mmol) dropwise. The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (50 mL), and then extracted with EtOAc (3x120 mL). The organic layer was dried and concentrated to give the crude product. This crude product was then purified by flash column chromatography using 30% EtOAc in hexane as eluent to give **5** as a white solid (4.23 g, 83.0%). LC-MS *m/z*: 404.1 (M+1).

Step 4: A mixture of 4-(trifluoromethoxy)phenylboronic acid (254 mg, 1.24 mmol), 3-bromo-N-[6-(2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-4-methyl-benzamide **5** (250 mg, 0.62mmol), $Pd(PPh_3)_4$ (36 mg, 0.03 mmol), Na_2CO_3 (2.0M aqueous solution, 1.23 mL, 2.4 mmol) and DME (4.5 mL) in a sealed tube was heated at 130°C overnight. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and concentrated to give the crude product which was then purified by preparative mass triggered HPLC (C_{18} column, eluted with CH_3CN-H_2O containing 0.05% TFA) to give N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide (183.5 mg, 61.1% yield). LC-MS *m/z*: 486.2 (M+1).

The resultant crystalline product (Form A) was converted to the amorphous form by dissolving in 3% w/w aqueous ethanol, and the resultant solution spray dried at about 150°C.

Form B was prepared by heating the amorphous form in an oven at 110°C for 2 hours.

In a further embodiment, the invention relates to a process step or steps, or an intermediate as described herein.

B Pharmaceutical Compositions

Test formulations of the invention
(creams, solution type)

Formulation code	Form B	Form C	Form D	Form E
Composition	[%]	[%]	[%]	[%]
Propylene Glycol	10.00	2.00	10.00	2.00
Diisopropyl adipate(DIPA)	15.00	15.00	15.00	15.00
Dimethyl isosorbide(DMI)	10.00	10.00	10.00	10.00
Benzyl alcohol	3.00	3.00	3.00	3.00
Butylhydroxyanisol	0.10	0.10	0.10	0.10
Butylhydroxytoluol	0.10	0.10	0.10	0.10
Triglyceride (MCT)	15.00	5.00	5.00	5.00
Stearyl alcohol	4.00	4.00	4.00	4.00
Cetyl alcohol	4.00	4.00	4.00	4.00
Glyceryl monostearate	2.00	2.00	2.00	2.00
Active compound*	0.75	0.75	0.75	0.25
Sodium cetylstearyl sulfate (Lanette E [®])	1.00	1.00	1.00	1.00
Carbopol 974P	X	0.50	0.20	0.50
Nanopure water	35.05	48.65	43.15	49.15
Sodium Hydroxide 1M	X	3.90	1.70	3.90
Total	100.00	100.00	100.00	100.00

5 Comparator formulations:

formulation XD (cream solution type)	
Excipient	Amount [%]
Active compound*	0.5
medium chain triglyceride (MCT)	20
Sodium cetylstearyl sulfate	1
Cetyl alcohol	4
Stearyl alcohol	4
Glycerolmonostearat	2
Benzyl alcohol	5
Polysorbate 80	2
Water	61.5

Formulation XF (cream solution type)	
Excipient	Amount [%]
Active compound*	0.4
medium chain triglyceride (MCT)	20
DIPA	15
Transcutol	10
Sodium cetylstearyl sulfate	1
Cetyl alcohol	4
Stearyl alcohol	4
Glyceroimonostearat	2
Benzyl alcohol	1
Butylated hydroxytoluene	0.1
Water	42.5

Formulation XH (cream solution type)	
Substance	Amount [g]
Mid chain triglycerides	5
Di isopropyl adipate	15
Propylene glycol	10
Oleyl alcohol	10
Sodium cetylstearyl sulfate	1
Cetyl alcohol	4
Stearyl alcohol	4

Glycerol monostearat	2
Benzyl alcohol	3
BHT	0.1
BHA	0.1
Active compound*	0.5
Water	45.3

* "active compound" means 2-Methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide

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In vitro human skin penetration/permeation assay

Ca. 300 mg or 300 μ L of formulation were applied on each skin punch (thawed samples of human abdominal cadaver skin dermatomized to a thickness of 500 μ m). The integrity of the skin was determined by evaluating the permeation of tritiated water. Formulations were tested on skin samples having similar $^3\text{H}_2\text{O}$ permeation. The receptor chamber was filled with a mixture of phosphate buffered saline and fetal bovine serum (2+1, v/v; pH=7.4) as receiver solution (Gibco BRL, CH) to simulate the human physiological conditions and the systemic removal of the drug from skin. The receiver solution contained 100 U/mL of 1 % penicillin/strepto-mycine mixture to prevent microbiological contamination. The temperature of the cells was kept at $34\pm 1^\circ\text{C}$.

200 μ L of receiver solution was sampled/cell and replaced at each occasion with the same volume of blank solution in order to keep the total buffer volume constant during the assay period. The time points investigated were 4, 7, 20, 24, 28, 32, 44 and 48 h after application.

At the end of the experiment, the residual formulation on the surface of each skin sample was removed. The stratum corneum was separated from the epidermis/dermis by 20 strippings, and biopsies of the treated area of the stripped skin were taken. The drug content in the receptor fluids and stripped skin was assessed by LC/MS/MS.

The flux was calculated by linear regression analysis from the slope of the linear portion of the concentration-vs.-time plot. In addition, the cumulative drug amount permeated was assessed.

Fig 1 shows the skin concentrations (penetration), where formulation A is a reference formulation of 1.0 % active compound in ethanol/PEG (polyethylene glycol) 30/70.

Formulations B, D and E give similar, good skin penetration levels. Unexpectedly, following application of formulation C, even higher skin penetration levels are obtained.

The following formulations XD, XF and XH were also tested against formulation B in the in-vitro human skin penetration assay. The results show that all the tested formulations provide acceptable skin penetration levels, however formulation B provides an unexpectedly good level of skin penetration.

Formulation	Skin concentration after 48h (ng/cm ²)	Skin concentration after 48h (ng/g)
XD	55	860.0
XF	132	1690.0
XH	60	910.0
B	168	2120.0

In Vivo tests

1. Test for penetration into the skin of domestic pigs ("4cm² assay")

- 5 Method: The "4cm² assay" is used to measure the time-dependent penetration of an epicutaneously applied compound into the dermis of juvenile domestic pigs. The animals (weighing 12 – 18 kg) are placed in a humane restraint sling for treatment. The pharmaceutical compositions, solution type, as prepared above, were applied once to different small areas (4cm²) on the dorsolateral back at 8, 6, 4, 2, 1 and 0.5 hrs prior to euthanasia and
- 10 dissection of the treated skin samples. Next, heated metal blocks were placed on the treated skin flaps for 1 min and the loosened epidermis was peeled off with forceps. From the de-epidermized skin flap 1 mm thick dermal sheets were prepared with a dermatome from which 6mm punch biopsies were collected and analysed for time-dependent test compound concentration by LC/MS. The procedure described was done with careful avoidance of
- 15 contamination of the dermal samples with superficially attached test compound.

Results: The following table provides Area Under the Curve (AUC) values of the agent of the invention in pig dermis when applied epicutaneously in the identified compositions.

Formulation	AUC 0-8 h [$\mu\text{g}\cdot\text{h}/\text{g}$] Mean (SEM)+
B (0.75%)	2.0 (0.47)
C (0.75%)	3.0 (0.87)
D (0.75%)	3.1 (0.68)

+ : Values from 8 dermal samples per formulation and time point (4 pigs, 2 samples each)

The results of the "4 cm² assay" confirm the good penetration into the skin of the agent of the invention following application of compositions B, C and D under *in-vivo*-conditions.

- 5 Fig 2 shows the levels of active compound in de-epidermized pig skin 24 hrs after epicutaneous application of different formulations. Following application of Formulation B, an unexpected improvement in the dermal concentration of active compound is observed, compared to the comparator formulations. The levels are dose-proportionally high.

Formulation	Compound levels in pig dermis 24hrs after application (ng/g) Mean (SEM)+
XF 0.4%	407 (97)
XH 0.5%	517 (77)
B 0.75%	1,007 (153)
XD 0.5%	340 (52)

10 +Mean of 6 samples per formulation (3 animals, 2 dermal samples each)

2. Test for permeation through the skin of domestic pigs (10% BSA-assay)

5 Method: The primary objective of the "10%BSA-assay" is to assess the percutaneous absorption (permeation through the skin) of a formulated compound after application to 10% body surface area (BSA) in juvenile, 12 – 18 kg weighing pigs. In addition, dermal levels of the treated skin are determined at termination (24 hrs after application). The formulation is applied in volumes of 5 ml to 400 cm² dorsal area (equivalent to 10% BSA of a 10 kg animal).
10 Blood samples are collected from a jugular vein 0.5, 1, 2, 4, 8, and 24 hrs after the application. Dermal samples from the treated skin are prepared as described.

Results: After application of formulations XF (0.45%), XH (0.5%), XD (0.5%) and B (0.75%) levels of active compound were in most plasma samples below LLOQ (0.1 ng/ml). The
15 fewest positive samples with the lowest levels were detected in XH and B-treated animals. Highest and most frequent levels were detected in XD-treated animals. The levels were 0.29 (SEM:0.11) and 0.08 (SEM: 0.04) ng/ml at 0.5 and 1 hrs after application, respectively. At later time points the levels were below LLOQ.

3. Test for efficacy in treatment of BCCs (basal cell carcinomas)

20 **Methods:** A total of 8 Gorlin's Syndrome patients, presenting 27 BCCs, were treated b.i.d. with Formulation B or with vehicle for 4 weeks. The vehicle is a formulation equivalent to Formulation B except that the active compound is replaced by an equivalent percentage of
25 water.

Results: The Formulation B was well tolerated and showed no potential for skin irritation. Plasma concentrations of the active compound after 4 weeks' treatment were below detection level (0.05ng/mL) in 4/8 patients (highest plasma level detected was 0.11ng/mL). Mean skin concentrations of the active compound were 737ng/g (BCC) and 605ng/g
30 (uninvolved skin). BCCs treated with the Formulation B (n=13) showed complete clinical response in 3, partial response in 9 and no response in 1 BCC. Except for one partial response, the vehicle produced no clinical response in any of the 14 treated BCC's.

Mean volume reductions of 49.8% were observed in the BCCs treated with Formulation B vs. 9.1% with the vehicle treatment; mean surface area reductions were
35 40.8% and 10.5%, respectively (3D digital photography). Histologically, the residual tumor cells nests showed an average 60% reduction of Ki-67 proliferating cells in the lesions treated with Formulation B vs. vehicle. Biomarker analysis showed that, except for one

patient, Gli 1, Gli 2, Ptch 1 and Ptch 2 mRNA level reductions correlated with clinical outcome.

Conclusions: These results demonstrate that the formulations of the invention are effective in the treatment of BCCs in Gorlin's Syndrome patients. Since the use of other currently
5 available topicals for treatment of BCCs is limited by skin irritation, treatment with formulations of the present invention in NBCCS patients may offer a significant and unexpected advantage.

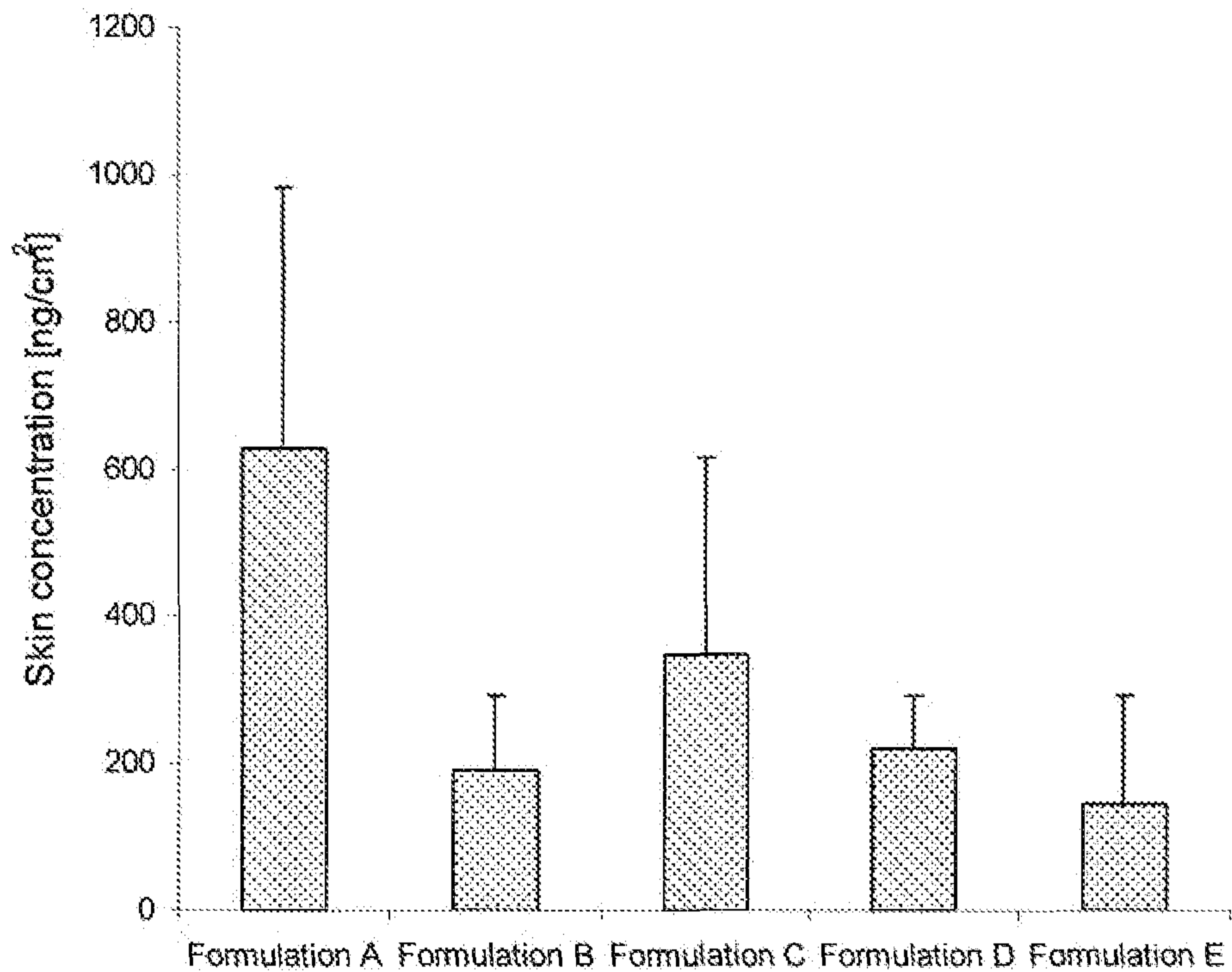
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CLAIMS:

1. A topical pharmaceutical composition comprising
 - a) N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide;
 - 5 b) dimethylisosorbide (DMI); and
 - c) an oily phase.
2. A composition as claimed in claim 1 further comprising diisopropyl adipate (DIPA).
3. A composition as claimed in claim 1, wherein the dimethylisosorbide (DMI)
10 in a range of from 5.0 to 15.0 wt%.
4. A composition as claimed in claim 2, wherein the diisopropyl adipate (DIPA) is present in the range of from 10.0 to 20.0 wt%.
5. A composition as claimed in claim 2, further comprising propylene glycol in the range of from 0.5 to 20 wt%.
- 15 6. A composition as claimed in any one of claims 1 to 5, further comprising benzyl alcohol in an amount of up to 10 wt%.
7. A composition as claimed in claim 1, wherein the oily phase is a mid chain triglyceride.
8. A composition as claimed in claim 1, for use in the treatment of Gorlin's
20 syndrome or basal cell carcinoma.

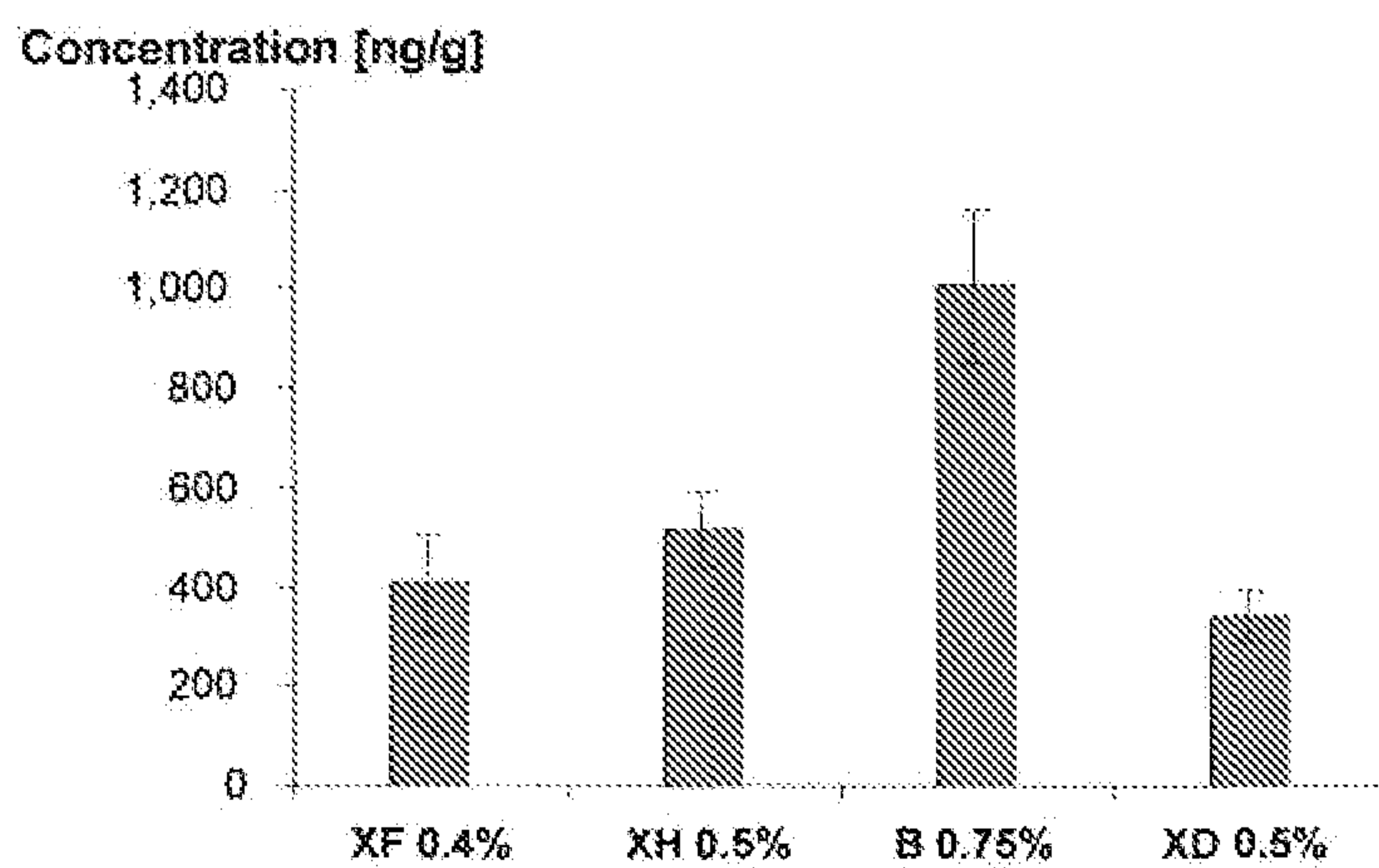
FIG 1



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Fig 2

Mean values ± SEM



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15

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Fig 3

