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EP-A- 1 282 084
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BARTROLI J ET AL: "NEW AZOLE ANTIFUNGALS. 3. SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 3-SUBSTITUTED-4(3H)-QUINAZOLINONES", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, 29 April 1998 (1998-04-29), pages 1869-1882, XP001106675, ISSN: 0022-2623
SORBERA, L. A. ET AL: "Albaconazole : antifungal", DRUGS OF THE FUTURE , 28(6), 529-537 CODEN: DRFUD4; ISSN: 0377-8282, 2003, XP002461045,
CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1998, pages 163-208, XP001156954, ISSN: 0340-1022

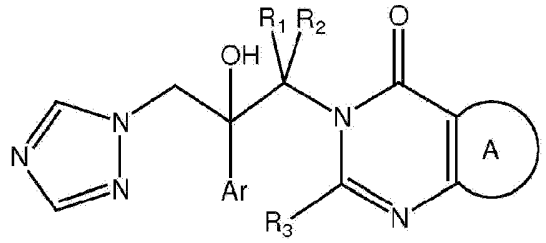
DESCRIPTION

FIELD OF THE INVENTION

[0001] The present subject matter relates to a novel crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-quinazolin-4(3H)-one, and pharmaceutical compositions containing the crystalline form. The present subject matter relates to the specific crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one.

BACKGROUND OF THE INVENTION

[0002] U.S. Patent No. 5,807,854 discloses various novel antifungal compounds of the formula I:



I

methods of making these compounds, pharmaceutical compositions containing these compounds, and their use in the treatment or prevention of fungal infections in animals. One of the specifically exemplified compounds falling within this genus is albaconazole, which also has the chemical name (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. However, this patent does not disclose, refer to, or even suggest the benefits to obtaining specific crystalline forms of the compounds of formula I.

[0003] To prepare pharmaceutical compositions containing (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4-(3H)-one for administration to mammals in accordance with exacting health registration requirements of the U.S. and international health registration authorities, e.g. the U.S. Food and Drug Administration's Good Manufacturing Practice ("GMP") requirements, there is a need to produce (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4-(3H)-one in as pure a form as possible, especially a form having constant and consistent physical properties.

[0004] A process for the preparation of pyrimidone derivates useful as antifungal agents is known from EP 1 282 084 A2.

[0005] Further, the synthesis and antifungal activity of 3-substituted-4(3*H*)-quinazolinones has

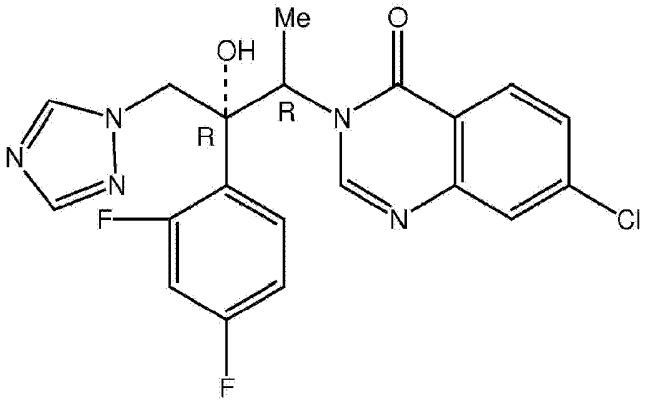
been described by Bartroli et al. (J. Med. Chem. 1998, 41, 1869-1882).

[0006] Further, the antifungal activity of albaconazole has been confirmed by Sorbera et al. (Drugs of the Future 2003), 28 (6): 529-537).

[0007] Further, crystalline polymorphism of organic compounds have been described by Caira (Topics in Current Chemistry, Vol. 198 Springer Verlag Berlin Heidel-berg 1998).

SUMMARY OF THE INVENTION

[0008] Accordingly, the present subject matter provides various crystalline forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-tria-zol-1-yl)propyl]quinazolin-4(3H)-one represented by formula II:



II

[0009] This compound was previously known to exist in an amorphous form. It has now been recognized that the compound can exist as one of six crystalline forms that are presently identified. Accordingly, a crystalline form of this compound is contemplated herein, such as a pure crystalline form substantially devoid of the compound's amorphous form and any residual solvent. In this regard, substantially pure crystalline form of Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one are contemplated herein.

[0010] In this regard, a preferred embodiment of the present subject matter relates to a crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising the reaction product of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one and an organic solvent. In a further preferred embodiment, the present subject matter relates to a crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising the reaction product of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-tria-zol-1-yl)propyl]quinazolin-4(3H)-one and an organic solvent in the presence of water.

[0011] The subject matter relates to a substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one that is Form III.

[0012] Still, the present subject matter relates to a pharmaceutical composition comprising an anti-microbially or anti-fungally effective amount of a substantially pure crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one or a pharmaceutically acceptable salt or derivative thereof and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE FIGURES

[0013]

Fig. 1 presents a characteristic XRPD pattern of the crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one.

Fig. 2 presents a characteristic IR spectrum of the crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one.

Fig. 3 presents a characteristic DSC thermogram of the crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one.

DETAILED DESCRIPTION OF THE INVENTION

[0014] As used herein, the terms "administering", "administration", and like terms refer to any method which, in sound medical or cosmetic practice, delivers the composition to a subject in such a manner as to provide a therapeutic effect.

[0015] The phrase "aqueous solvent" as used herein refers to a solvent such as water or containing water. Other dissolved components may be present in small amounts, such as, for example, salts, buffers, and other components understood by one of ordinary skill in the art to be optionally present in an aqueous solution.

[0016] The phrase "crystalline form" as used herein refers to crystals of the same molecule having different physical properties as a result of the order of the molecules in the crystal lattice. Accordingly, as used herein the phrase "crystalline form" is intended to refer to different crystalline forms, polymorphs, pseudopol-ymorphs, and solvate forms of a single molecular

entity. Different crystalline forms of a single compound may have different chemical, physical, mechanical, electrical, thermodynamic, and/or biological properties from each other. The differences in physical properties exhibited by crystalline forms affect pharmaceutical parameters such as storage stability, compressibility, density (important in formulation and product manufacturing), dissolution rates (an important factor in determining bio-availability), solubility, melting point, chemical stability, physical stability, powder flowability, compaction, and particle morphology. Each separate crystalline form of an individual compound will exhibit consistent chemical, physical, mechanical, electrical, thermodynamic, and biological properties.

[0017] The phrase "derivative" as used herein refers to any hydrate, solvate, salt, racemate, isomer, enantiomer, prodrug, metabolite, ester, or other analog or derivative of a particular chemical compound or molecule. The term "derivative" may also mean a modification to the disclosed compounds including, but not limited to, hydrolysis, reduction, or oxidation products, of the disclosed compounds. Hydrolysis, reduction, and oxidation reactions are known in the art.

[0018] Differences in stability can result from changes in chemical reactivity (e.g. differential oxidation, such that a dosage form discolors more rapidly when comprised of one crystalline form than when comprised of another crystalline form) or mechanical changes (e.g. tablets crumble on storage as a kinetically favored crystalline form converts to thermodynamically more stable crystalline form) or both (e.g. tablets of one crystalline form are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, some crystalline form transitions affect potency and/or toxicity. In addition, the physical properties of the crystal may be important in processing; for example, one crystalline form might be more likely to form solvates or might be difficult to filter and wash free of impurities (i.e. particle shape and size distribution might be different between one crystalline form relative to the other).

[0019] As used herein, the phrases an "effective amount" or a "therapeutically effective amount" of an active agent or ingredient, or pharmaceutically active agent or ingredient, which are synonymous herein, refer to an amount of the pharmaceutically active agent sufficient enough to have a therapeutic effect upon administration. A therapeutically effective amount of the pharmaceutically active agent may, will, or is expected to cause a relief of symptoms. Effective amounts of the pharmaceutically active agent will vary with the particular condition or conditions being treated, the severity of the condition, the duration of the treatment, the specific components of the composition being used, and like factors.

[0020] As used herein, the phrase "pharmaceutically acceptable salts" refers to salts of certain ingredient(s) which possess the same activity as the unmodified compound(s) and which are neither biologically nor otherwise undesirable. A salt can be formed with, for example, organic or inorganic acids. Non-limiting examples of suitable acids include acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentanepropionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, formic acid, fumaric acid, glyceric acid, glycerophos-phoric acid, glycine, glucoheptanoic acid,

gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthylanesulfonic acid, naphthylic acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosylic acid, undecylenic acid, and naturally and synthetically derived amino acids.

[0021] If organic bases are used, poorly volatile bases are preferably employed, for example low molecular weight alkanolamines such as ethanolamine, diethanolamine, N-ethylethanolamine, N-methyldiethanolamine, triethanolamine, diethylaminoethanol, 2-amino-2-methyl-n-propanol, dimethylaminopropanol, 2-amino-2-methylpropanediol, and triisopropanolamine. Ethanolamine is particularly preferred in this regard. Further poorly volatile bases which may be mentioned are, for example, ethylenediamine, hexamethylenediamine, morpholine, piperidine, piperazine, cyclohexylamine, tributylamine, dodecylamine, N,N-dimethyldodecylamine, stearylamine, oleylamine, benzylamine, dibenzylamine, N-ethylbenzylamine, dimethylstearylamine, N-methylmorpholine, N-methylpiperazine, 4-methylcyclohexylamine, and N-hydroxyethylmorpholine.

[0022] Salts of quaternary ammonium hydroxides such as trimethylbenzylammonium hydroxide, tetramethylammonium hydroxide, or tetraethylammonium hydroxide can also by used, as can guanidine and its derivatives, in particular its alkylation products. However, it is also possible to employ as salt-forming agents, for example, low molecular weight alkylamines such as methylamine, ethylamine, or triethylamine. Suitable salts for the components to be employed according to the present subject matter are also those with inorganic cations, for example alkali metal salts, in particular sodium, potassium, or ammonium salts, alkaline earth metal salts such as, in particular, the magnesium or calcium salts, as well as salts with bi- or tetravalent cations, for example the zinc, aluminum, or zirconium salts. Also contemplated are salts with organic bases, such as dicyclohexylamine salts; methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; asthma halides, such as benzyl and phenethyl bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

[0023] The phrase "reaction product" as used herein refers to any crystalline form obtained from the processes described herein, including but not limited to anhy-drates, hydrates, polymorphs, solvates, N-oxides, and/or salts of these crystalline forms.

[0024] The phrase "substantially pure" as used herein refers to an individual crystalline form which is substantially devoid of all other crystalline forms, as well as degradation products of the crystalline form, the amorphous form, and any residual solvent, and is at least 85% pure on

a % weight basis, unless otherwise specified. Preferably, the crystalline form has at least 90% purity on a % weight basis. More preferably, the crystalline form has at least 93% purity on a % weight basis. Yet more preferably, the crystalline form has at least 95% purity on a % weight basis. Yet even more preferably, the crystalline form has at least 97% purity on a % weight basis.

[0025] The term "treating" as used herein refers to the process of producing an effect on biological activity, function, health, or condition of an organism in which such activity is maintained, enhanced, diminished, or applied in a manner consistent with the general health and well-being of the organism.

[0026] Other terms as used herein are meant to be defined by their well-known meanings in the art.

Crystalline Forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one

[0027] Six different crystalline forms of the compound (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one have presently been identified: crystalline Forms I, II, III, IV, V, and VI. Of these different crystalline forms, the most preferred will provide an antifungal, antimicrobial drug having the lowest impurity content, most consistent product quality, most consistent physical characteristics including color, rate of dissolution, and ease of handling, and greatest long term stability in comparison to the other crystalline forms or the amorphous form.

[0028] These crystalline forms, namely Forms I-VI, were identified as six distinct crystal forms. Certain physical characteristics of these crystalline forms generated during crystallization studies, are as follows:

- Form I: typically obtained by crystallizing the amorphous form using supercritical CO_2 crystallization conditions. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a characteristic DSC profile.
- Form II: typically obtained by crystallizing the amorphous form using supercritical CO_2 crystallization conditions. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a characteristic DSC profile.
- Form III: typically obtained under standard crystallization conditions using a variety of solvents such as ethanol, ethyl acetate, dichloromethane, and a combination of ethanol and ethyl acetate. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a DSC profile with a strong endothermic peak onset at about 99°C. No degradation products of form III were detected after 6 months of storage at 30°C/65% RH and 25°C/60% RH.
- Form IV: typically obtained by first dissolving any form in ethanol, then suspending this solution in water and stirring for a certain amount of time. This form may also be

obtained directly from the amorphous form or Forms III or VI of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one after storage for an extended period of time, for example after storage for 3 months at 40°C and 75% RH, as some but not all of the original form converts to Form IV. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a DSC profile with a strong endothermic peak onset at about 121°C.

- Form V: typically obtained under standard crystallization conditions, typically by first dissolving the amorphous form in ethyl acetate, then adding hexane to this solution. Diethyl ether can then be optionally added. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a DSC profile with a strong endothermic peak onset at about 108°C. Form V can best be characterized as a crystalline phase containing between about 2 and about 7% by weight of ethyl acetate and about 0.5 to about 2.5% by weight of hexane.
- Form VI: typically obtained by slurrying (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one in aqueous ethanol or by slowly cooling a saturated aqueous ethanol solution that was seeded. This form may be obtained when the slurry comprises any other Form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl] quinazolin-4(3H)-one, such as, for example, the amorphous form, Form III, Form IV, Form V, or combinations thereof. Complete conversion of a Form III slurry at 45°C to Form VI was noted after 3 hours in ethanol-water (1:9). High water activities are preferred for preparing Form VI to ensure that Forms III and/or V are not generated. This form displays a characteristic XRPD pattern, a characteristic IR spectrum, and a DSC profile with a strong endothermic peak ranging from about 102°C to 108°C. Form VI can best be characterized as a non-hygroscopic monohydrate.

Purity

[0029] The present subject matter contemplates substantially pure and/or isolated crystallin Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. In this regard, the present subject matter contemplates the crystalline form which is substantially devoid of the amorphous form and of any residual solvent on a weight % basis, except as otherwise noted herein. In a preferred embodiment, the present subject matter particularly contemplates the crystalline form free of any residual solvent, except as otherwise noted herein. Notwithstanding the above, crystalline form contemplated herein may be in a hydrated form and thus may contain a certain amount of water. In preferred embodiments in this regard, crystalline form may be formed as hydrate containing about 10% or less of water. In an alternative preferred embodiment, the present subject matter contemplates the crystalline form further substantially devoid of the other crystalline forms.

[0030] In a preferred embodiment, the substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has less than about 10% by weight of a different crystalline form or an amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a % weight basis.

[0031] In another preferred embodiment, the substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has at least 90% purity as defined by X-ray powder diffraction.

[0032] In another embodiment, the substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has less than about 10% by weight of any residual solvent.

[0033] For example, the present subject matter contemplates crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which has less than about 10% by weight of any residual solvent and the amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis; Accordingly, the present subject matter contemplates the crystalline form having at least 90% purity as defined by X-ray powder diffraction.

[0034] In an alternative example, the present subject matter further contemplates crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which also has less than about 10% by weight of the crystalline forms I, II, IV, V, or VI of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis;

[0035] In a preferred embodiment, the present subject matter contemplates the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which have less than about 7% by weight of any residual solvent and the amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis, or have a 93% purity as defined by X-ray powder diffraction. In an alternative preferred embodiment in this regard, the present subject matter may further contemplate the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which also have less than about 7% by weight of the other crystalline forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis.

[0036] In a particularly preferred embodiment, the present subject matter contemplates the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which have less than about 5% by weight of any

residual solvent and the amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis, or have a 95% purity as defined by X-ray powder diffraction. In an alternative preferred embodiment in this regard, the present subject matter may further contemplate the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which also have less than about 5% by weight of the other crystalline forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one as determined on a weight % basis.

[0037] In another preferred embodiment, the present subject matter contemplates the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which have less than about 10% by weight of any residual solvent. In a further preferred embodiment in this regard, the present subject matter contemplates the crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one which have less than 7%, more preferably less than 5% by weight, of any residual solvent.

[0038] The substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has a characteristic X-ray powder diffraction (XRPD) pattern 2-theta positions at about 4.08, 5.73, 6.22, 7.77, 8.15, 8.80, 11.25, 11.47, 12.44, 13.09, 15.57, 17.63, 18.66, 20.85, 26.65, and 27.12 +/- 0.2.

[0039] In another embodiment, the substantially pure crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has a characteristic X-ray powder diffraction (XRPD) pattern that may contain at least one 2-theta position selected from the group consisting of those at about 4.08, 5.73, 6.22, 7.77, 8.15, 8.80, 11.25, 11.47, 12.44, 13.09, 14.33, 14.68, 14.89, 15.57, 16.35, 16.68, 17.27, 17.63, 18.66, 19.32, 20.85, 22.12, 22.49, 23.58, 24.63, 25.02, 26.65, 27.12, 28.74, 29.11, 29.81, 31.35, and 33.48+/-0.2.

[0040] The substantially pure crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has a characteristic X-ray powder diffraction (XRPD) pattern that may contain at least one 2-theta position selected from the group consisting of those at about 4.08, 5.73, 6.22, 7.77, 8.15, 8.80, 11.25, 11.47, 12.44, 13.09, 15.57, 17.63, 18.66, 20.85, 26.65, and 27.12 +/- 0.2. In other preferred embodiments, the substantially pure crystal Form III has two or more of the XRPD peaks identified above. In further embodiments, the crystal form has three or more of the XRPD peaks identified above. In yet further embodiments, the crystal form has four or more of the XRPD peaks identified above.

[0041] In one embodiment, the substantially pure crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one has an infrared spectra pattern that may contain at least one spectral line position selected from the group consisting of those at 1677.0, 1600.0, 1557.5, 1498.3, 1462.6, 1403.0, 1318.4,

1272.5, 1254.1, 1170.0, 1138.7, 1101.6, 1060.2, 1016.4, 966.7, 932.7, 902.4, 855.5, 801.5, 785.8, 694.0, 677.9, 665.4, 631.7, 532.7, and 411.6 cm^{-1}.

[0042] In other preferred embodiments, the crystal form has two or more of the XRPD peaks identified in any one of the embodiments disclosed herein. In further embodiments, the crystal form has three or more of the XRPD peaks identified in any one of the embodiments disclosed herein. In yet further embodiments, the crystal form has four or more of the XRPD peaks identified in any one of the embodiments disclosed herein.

[0043] In another embodiment, the substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one is characterized by at least one of the following properties: an X-ray powder diffraction pattern substantially similar to that presented in the figure 1; a differential scanning calorimetry thermogram substantially similar to that presented in the figure 3.

[0044] In a preferred embodiment, the substantially pure crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one is characterized by at least one of the following properties: a differential scanning calorimetry thermogram exhibiting a large endo-therm at about 102°C, and having an onset temperature at about 87°C; or an infrared spectra having characteristic infrared spectral peak positions at 1607, 1555, 1468, 1400, 1361, 1316, 1280, 1218, 1165, 1102, 1014, 976, 938, 760, and 698 cm^{-1}. In one preferred embodiment, the substantially pure crystalline form is characterized as having an infrared spectra having at least two of the characteristic infrared spectral peak positions at 1607, 1555, 1468, 1400, 1361, 1316, 1280, 1218, 1165, 1102, 1014, 976, 938, 760, and 698 cm^{-1}. In another preferred embodiment, the substantially pure crystalline form is characterized as having an infrared spectra having at least three of the characteristic infrared spectral peak positions. In yet another preferred embodiment, the substantially pure crystalline form is characterized as having an infrared spectra having at least four of the characteristic infrared spectral peak positions.

[0045] Additionally, the present subject matter contemplates substantially pure crystalline forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one substantially devoid of degradation products of the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. In this regard, the present subject matter further contemplates a substantially pure crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one having not less than 97% purity with respect to other forms of the compound or any degradation products.

Form III

[0046] Crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-

3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one was in part identified by its characteristic XRPD pattern. The XRPD pattern for Form III was measured at room temperature using a Philips X'Pert diffractometer equipped with a θ/2θ goniometer, a Cu tube working at 50 kV and 40 mA (CuKα radiation, λ = 1.5419 Å), a divergence slit = 1/4°, Soller slits = 0.04 rad, an anti-scatter slit = 1/4°, a receiving slit = 0.10 mm, and a secondary curved graphite monochromator. Data were collected in the range 2-35° of 2theta using a step-scan technique with a step size = 0.02° and a time per step = 20 s.

[0047] A characteristic XRPD pattern distinctive to Form III was observed, as represented by Fig.1. The characteristic 2-theta positions and corresponding intensities observed for this specific pattern are summarized below in Table1.

TABLE 1

Characteristic XRPD 2-Theta Positions and Intensities for Form III	
Characteristic XRPD 2-theta positions (+/-0.2)	**Characteristic XRPD Relative Intensity (%)**
4.08	51
5.73	34
6.22	13
7.77	36
8.15	60
8.80	30
11.25	61
11.47	29
12.44	48
13.09	17
14.33	46
14.68	98
14.89	60
15.57	68
16.35	43
16.68	58
17.27	29
17.63	40
18.66	100
19.32	12
20.85	71
22.12	25
22.49	18

Characteristic XRPD 2-Theta Positions and Intensities for Form III	
Characteristic XRPD 2-theta positions (+/-0.2)	**Characteristic XRPD Relative Intensity (%)**
23.58	29
24.63	20
25.02	24
26.65	48
27.12	77
28.74	15
29.11	17
29.81	23
31.35	10
33.48	8

[0048] The most relevant 2-theta positions and corresponding intensities observed for this specific XRPD pattern for Form III are summarized below in Table2.

TABLE 2

Most Relevant XRPD 2-Theta Positions and Intensities for Form III	
Characteristic XRPD 2-theta positions (+/-0.2)	**Characteristic XRPD Relative Intensity (%)**
4.08	51
5.73	34
6.22	13
7.77	36
8.15	60
8.80	30
11.25	61
11.47	29
12.44	48
13.09	17
15.57	68
17.63	40
18.66	100
20.85	71
26.65	48
27.12	77

[0049] A set of XRPD peaks that uniquely characterizes Form III has 2-theta positions at about 4.08, 5.73, 6.22, 7.77, 8.15, 8.80, 11.25, 11.47, 12.44, 13.09, 15.57, 17.63, 18.66, 20.85, 26.65, and 27.12 +/- 0.2.

[0050] The complete infrared spectrum of the crystalline Form III is shown in Fig. 2 and is characterized as summarized below in Table3.

TABLE 3

Infrared Spectrum for Form III
Frequency (cm^{-1}) (+/-0.1)
1677.0
1600.0
1557.5
1498.3
1462.6
1403.0
1318.4
1272.5
1254.1
1170.0
1138.7
1101.6
1060.2
1016.4
966.7
932.7
902.4
855.5
801.5
785.8
694.0
677.9
665.4
631.7
532.7
411.6

[0051] Form III was further observed to have a characteristic endothermic peak onset observed at about 99 +/- 5 degrees C using DSC analysis, as represented by Fig.3.

Data Collection

[0052] A colorless needle of $C_{20}H_{16}ClF_2N_5O_2,H_2O$ was isolated from 1:1 ethanol-water slurry and the structure determined by single crystal X-ray diffraction. The needle having approximate dimensions of 0.45 x 0.13 x 0.13 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed using Mo Kα radiation (λ = 0.71073Å) on a Nonius KappaCCD equipped with a graphite crystal, incident beam monochromator.

[0053] Cell constants for data collection were obtained from least-squares refinement, using the setting angles of 6937 reflections in the range $3 < \theta < 25°$. The refined mosaicity from DENZO/SCALEPACK (Z. Otwinowski and W. Minor, Methods Enzymol., 276, 307, 1997, the contents of which are hereby incorporated by reference in their entirety) was 1.24° indicating poor crystal quality. The space group was determined by the program XPREP (XPREP in SHELXTL version 6.12, Bruker AXS Inc., Madison, Wisconsin, USA, 2002, the contents of the program, and user manuals of the program, are hereby incorporated by reference in their entirety.) From the systematic presences of h00 h=2n, 0k0 k=2n, 00l l=2n, and from subsequent least-squares refinement, the space group was determined to be $P2_12_12_1$ (No. 19).

[0054] The data were collected at a temperature of 150K. Data were collected to a maximum 2θ of 50.1°.

Data Reduction

[0055] A total of 6937 reflections were collected, of which 3516 were unique. Frames were integrated with DENZO-SMN (Z. Otwinowski and W. Minor, Methods Enzymol., 276, 307, 1997).

[0056] Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 2.3 /cm for Mo Kα radiation. An empirical absorption correction using SCALEPACK (Z. Otwinowski and W. Minor, Methods Enzymol., 276, 307, 1997) was applied. Transmission coefficients ranged from 0.934 to 0.970. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 14.2% based on intensity.

Structure Solution and Refinement

[0057] The structure was solved by direct methods using SIR2004 (M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giaco-vazzo, G. Polidori, and R. Spagna., J. Appl. Cryst., 38, 381, 2005, the contents of which are hereby incorporated by reference in their entirety). The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares by minimizing the function:

$$\sum w\left(|F_o|^2 - |F_c|^2\right)^2$$

[0058] The weight w is defined as $1/[\sigma^2(F_o^2)+1.9322P]$ where $P=(F_o^2+2F_c^2)/3$

[0059] Scattering factors were taken from the "International Tables for Crystallography" ("International Tables for Crystallography", Vol. C, Kluwer Academic Publishers, Utrecht, The Netherlands, 1992, Tables 4.2.6.8 and 6.1.1.4., the contents of which are hereby incorporated by reference in their entirety). Of the 3516 reflections used in the refinements only 2654 reflections with $F_o^2>2\sigma(F_o^2)$ were used in calculating *R1*. The final cycle of refinement included 293 variable parameters and converged (largest parameter shift was <0.01 times its estimated standard deviation) with unweighted and weighted agreement factors of:

$$R = \sum |F_o - F_c| / \sum F_o = 0.069$$

$$R_w = \sqrt{\left(\sum w\left(F_o^2 - F_c^2\right)^2 / \sum w\left(F_o^2\right)^2\right)} = 0.102$$

[0060] The standard deviation of an observation of unit weight was 1.09. The highest peak in the final difference Fourier had a height of 0.26 e/A^3. The minimum negative peak had a height of -0.30 e/A^3. The factor for the determination of the absolute structure (H. D. Flack, Acta Cryst., A39, 876, 1983, the contents of which are hereby incorporated by reference in their entirety) refined to 0.02.

[0061] Refinement was performed on a LINUX PC using SHELX-97 (G. M. Sheldrick, SHELXL97. A Program for Crystal Structure Refinement. Univ. of Gottingen, Germany, 1997, the contents of the program, and user manuals of the program, are hereby incorporated by reference in their entirety). Crystallographic drawings were done using programs ORTEP (C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA, 1976 the contents of the report, the program, and user manuals of the program, are hereby incorporated by reference in their entirety) and Mercury (Mercury 1.4.1, Cambridge Crystallographic Diffraction Center, Cambridge, 2005, the contents of the program, and user manuals of the program, are hereby incorporated by reference in their entirety).

[0062] The orthorhombic cell parameters and calculated volume were: a = 12.0968(15)Å, b = 12.6245(16)Å, c = 13.3520(19)Å, α = β = γ = 90°, V = 2039.1(5)Å^3. For Z = 4 and formula weight = 449.85g/mol, the calculated density is 1.47 g/cm^3. The quality of the structure obtained was reasonable, as indicated by the R-value of 6.9%. Usually R-values in the range of 2 to 6% are quoted for the most reliably determined structures (J. Glusker, K. Trueblood, Crystal Structure Analysis: A Primer, 2nd ed.; Oxford University press: New York, 1985; p.87 , the contents of the entire book are hereby incorporated by reference in their entirety).

Pharmaceutical Compositions

[0063] In another preferred embodiment, the present subject matter relates to pharmaceutical compositions containing an anti-microbially or anti-fungally effective amount of the pure crystalline polymorph III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one or a pharmaceutically acceptable salt or derivative thereof, and a pharmaceutically acceptable carrier. In a particularly preferred embodiment, these pharmaceutical compositions comprise the pure crystalline Form III having a purity of at least 85% by weight, or not more than 15% by weight of other forms of the compound and any residual solvents. In a more preferred embodiment, these pharmaceutical compositions comprise the pure crystalline Form III having a purity of at least 90% by weight, with a purity of at least 95% by weight being most preferred. In another preferred embodiment, these pharmaceutical compositions comprise the pure crystalline Form III having a purity ranging from about 85% to 99.99% purity on a % weight basis. More preferably, the compositions comprise the crystalline form having a purity ranging from about 90% to 99.99% purity on a % weight basis. Further more preferably, the crystalline form has a purity ranging from about 93% to 99.99% purity on a % weight basis. Yet more preferably, the compositions comprise the crystalline form having a purity ranging from about 95% to 99.99% purity on a % weight basis. Yet even more preferably, the compositions comprise the crystalline form having a purity ranging from about 97% to 99.99% purity on a % weight basis

[0064] The phrase "pharmaceutically acceptable carrier" as used in this regard refers to any inactive ingredient present in one of the herein described compositions in an amount effective to enhance the stability, effectiveness, or otherwise of said composition. Non-limiting examples of such pharmaceutically acceptable carriers include diluents, excipients, suspending agents, lubricating agents, adjuvants, vehicles, delivery systems, emulsifiers, disintegrants, absorbants, adsorbents, preservatives, surfactants, colorants, flavorants, emollients, buffers, pH modifiers, thickeners, water softening agents, humectants, fragrances, stabilizers, conditioning agents, chelating agents, sweeteners, propellants, anticaking agents, viscosity increasing agents, solubilizers, plasticizers, penetration enhancing agents, glidants, film forming agents, fillers, coating agents, binders, antioxidants, stiffening agents, wetting agents, or any mixture of these components.

[0065] The carriers useful herein may further include one or more compatible solid or liquid

filler, diluents, or encapsulating materials which are suitable for human or animal administration.

[0066] Biocompatible carriers, as used herein, are components that do not cause any interactions which substantially reduce the efficacy of the pharmaceutical composition in an ordinary user environment. Possible pharmaceutical carriers must be of sufficiently low toxicity to make them suitable for administration to the subject of treatment.

[0067] Some non-limiting examples of substances which can serve as a carrier herein include sugar, starch, cellulose and its derivatives, powered tragacanth, malt, gelatin, talc, stearic acid, magnesium stearate, calcium sulfate, vegetable oils, polyols, alginic acid, pyrogen-free water, isotonic saline, phosphate buffer solutions, cocoa butter (suppository base), emulsifier as well as other non-toxic pharmaceutically compatible substances used in other pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, excipients, tabletting agents, stabilizers, antioxidants, and preservatives may also be present.

[0068] Any non-toxic, inert, and effective carrier may be used to formulate the compositions contemplated herein. Suitable pharmaceutically acceptable carriers, excipients, and diluents in this regard are well known to those of skill in the art, such as those described in The Merck Index, Thirteenth Edition, Budavari et al., Eds., Merck & Co., Inc., Rahway, N.J. (2001); the CTFA (Cosmetic, Toiletry, and Fragrance Association) International Cosmetic Ingredient Dictionary and Handbook, Tenth Edition (2004); and the "Inactive Ingredient Guide", U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of Management, http:/www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Examples of preferred pharmaceutically acceptable excipients, carriers and diluents useful in the present compositions include distilled water, physiological saline, Ringer's solution, dextrose solution, Hank's solution, and DMSO.

[0069] These additional inactive components, as well as effective formulations and administration procedures, are well known in the art and are described in standard textbooks, such as Goodman and Gillman's: The Pharmacological Bases of Therapeutics, 8th Ed., Gilman et al. Eds. Pergamon Press (1990) and Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, Pa. (1990). The carrier may comprise, in total, from about 0.1% to about 99.99999% by weight of the pharmaceutical compositions presented herein.

[0070] Preferred compositions herein can be in the form of oral or topical compositions. The oral compositions contemplated herein may take the form of tablets, capsules, soft-gels, hard gels, solutions, suspensions, powders, dispersible granules, cachets, combinations thereof, or any other oral pharmaceutical dosage form as would commonly be known in the art.

[0071] A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegration agents; it can also be an encapsulating material. In powders, the carrier can be a finely divided solid

which is in admixture with the active compound. In a tablet, the active compound can be mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the size and shape desired. Non-limiting examples of suitable solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, other cellulose derivatives, a low melting wax, cocoa butter, and the like.

[0072] Similarly, the topical compositions contemplated herein may take the form of a gel, cream, lotion, suspension, emulsion, aerosol, ointment, foam, mousse, shampoo, nail lacquer, nail product, vaginal product, combinations thereof, or any other topical pharmaceutical dosage form commonly known in the art. Other pharmaceutical and cosmetic treatment compositions known to those skilled in the art, including liquids and balms, are additionally contemplated as falling within the scope of the present subject matter. Further, the present subject matter contemplates applying any of these compositions with an applicator. Non-limiting examples of useful applicators in this regard include a pledget, a pad, and combinations thereof. Additionally, the present subject matter further contemplates that any of these topical compositions can be provided in a package of less than 5 g topical composition as a unit of use.

[0073] Emulsions, such as oil-in-water or water-in-oil systems, as well as a base (vehicle or carrier) for the topical formulation can be selected to provide effectiveness of the active ingredient and/or avoid allergic and irritating reactions (e.g., contact dermatitis) caused by ingredients of the base or by the active ingredient.

[0074] In severe cases, occlusive therapy may be useful herein. Covering the treated area with a nonporous occlusive dressing can increase the absorption and effectiveness of the compounds and compositions described herein. Usually, a polyethylene film (plastic household wrap) is applied overnight over cream or ointment, since a cream or ointment is usually less irritating than lotion in occlusive therapy. Plastic tapes may be impregnated with drug and are especially convenient for treating isolated or recalcitrant lesions; children and (less often) adults may experience pituitary and adrenal suppression after prolonged occlusive therapy over large areas.

[0075] Suitable gelling agents which may be useful in the present compositions include but are not limited to aqueous gelling agents, such as neutral, anionic, and cationic polymers, and mixtures thereof. Exemplary polymers which may be useful in the instant compositions include carboxy vinyl polymers, such as carboxypolymethylene. A preferred gelling agent is Carbopol® brand polymer such as is available from Noveon Inc., Cleveland, OH. Carbopol® polymers are high molecular weight, crosslinked, acrylic acid-based polymers. Carbopol® homopolymers are polymers of acrylic acid crosslinked with allyl sucrose or allylpen-taerythritol. Carbopol® copolymers are polymers of acrylic acid, modified by long chain (C10-C30) alkyl acrylates, and crosslinked with allyl-pentaerythritol.

[0076] Other suitable gelling agents include cellulosic polymers, such as gum arabic, gum tragacanth, locust bean gum, guar gum, xanthan gum, cellulose gum, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

Combination Therapy

[0077] In another preferred embodiment, the present preferred compositions may be used in combination with an additional pharmaceutical dosage form to enhance their effectiveness in treating a microbial or fungal infection or disorder. In this regard, the present preferred compositions may be administered as part of a regimen additionally including any other pharmaceutical and/or pharmaceutical dosage form known in the art as effective for the treatment of a microbial and/or fungal infection. Similarly, a pharmaceutically active ingredient other than those specified herein can be added to the present preferred compositions to enhance their effectiveness in treating a microbial and/or fungal infection or disorder. Accordingly, this additional pharmaceutically active ingredient or additional pharmaceutical dosage form can be administered to a patient either directly or indirectly, and concomitantly or sequentially, with the preferred compositions described herein.

[0078] In this regard, antimicrobial agents other than the (1R,2R)-7-chloro-3-[2-(2,4-di-fluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one discussed above are additionally contemplated as useful for combination therapy discussed herein. Included among these other antimicrobial agents are those selected from the group consisting of imidazoles, allylamines, triazoles, glucan synthase inhibitors, chitin synthase inhibitors, polyenes, griseofulvin, morpholine derivatives, triazines, pyrimidines, any other antimicrobial azole, pharmaceutically acceptable salts or derivatives thereof, and mixtures thereof. Other antimicrobial agents known in the art as effective upon administration to a patient are further contemplated as effective within the present subject matter.

[0079] In a preferred embodiment, these other antimicrobial agents are those selected from the group consisting of amorolfine, amphotericin B, bacitracin, benzalkonium chloride, benzethonium chloride, bifonazole, butenafine, butoconazole, chloroxine, cilofungin, chlordantoin, chlortetracycline, ciclopirox, clindamycin, clioqinol, clotrimazole, econazole, elubiol, faeriefungin, fezatione, fluconazole, flucytosine, fungimycin, gentamicin, griseofulvin, haloprogin, hexylresorcinol, itraconazole, ketoconazole, methylbenzethonium chloride, miconazole, mupirocin, naftifine, nikkomycin Z, nystatin, l-ofloxacin, oxiconazole, oxytetracycline, phenol, polymyxin B, pyrido[3,4-e]-1,2,4-triazine, pyrrolnitrin, quaternary ammonium compounds, salicylic acid, saperconazole, sulconazole, tea tree oil, terbinafine, terconazole, tetracyclines, thiabendazole, ticlatone, tioconazole, tolnaftate, triacetin, triclocarbon, triclosan, undecylenic acid, voriconazole, zinc and sodium pyrithione, a pharmaceutically acceptable salt or derivative thereof, and a mixture thereof. Combinations of any of the foregoing anti-microbial agents or their pharmaceutically acceptable salts or derivatives are contemplated herein.

[0080] In one embodiment in this regard, the present preferred compositions and the additional pharmaceutical dosage form can be administered to a patient at the same time. In an alternative embodiment, one of the present preferred compositions and the additional pharmaceutical dosage form can be administered in the morning and the other can be administered in the evening.

[0081] In another preferred embodiment, the presently described compounds can be administered to a patient in need thereof in multiple pharmaceutical dosage forms. This combination therapy may maximize the effectiveness of the present composition in treating a microbial or fungal infection or disorder. In one preferred embodiment in this regard, both an oral and a topical composition, each containing Form VI of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one, can be administered, either concomitantly or sequentially, to a patient suffering from a microbial and/or fungal infection or disorder. In the alternative, the oral and topical compositions can contain different amorphous and/or crystalline forms of the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one compound.

Methods of Production

[0082] The crystalline form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one can be prepared by a separate process to arrive at a separate crystalline form.

[0083] The present subject matter relates to a process for preparing a crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising recrystallizing (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one from a solution or suspension of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one in an organic solvent, particularly an organic solvent selected from the group consisting of ethanol, ethyl acetate, dichloromethane, and a combination of ethanol and ethyl acetate. In a most preferred embodiment, the organic solvent is ethanol. In a further preferred embodiment, the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one forms a solution in the organic solvent.

[0084] Further, the solution or suspension is preferably formed at a temperature of at least 40° C. This solution or suspension can then optionally be cooled to a temperature of about 10° C to about 20° C. Accordingly, the present subject matter relates to a crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising the reaction product of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one and an organic solvent, particularly an organic solvent selected from the group consisting of ethanol,

ethyl acetate, dichloromethane, and a combination of ethanol and ethyl acetate, with ethanol being most preferred. One of skill in the art would understand that combinations of two or more organic solvents, with or without water, may also be useful for the purpose of producing a crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. In a preferred embodiment, combinations of two or more organic solvents, without water, may also be useful for the purpose of producing a crystalline form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one in this regard.

[0085] In a further preferred embodiment in this regard, the present subject matter relates to a process for preparing a crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazo-lin-4(3H)-one comprising:

- Adding (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one to a solvent selected from the group consisting of ethanol, ethyl acetate, dichloromethane, and a combination of ethanol and ethyl acetate to form a solution or suspension; and
- Crystallizing a crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one from said solution or suspension.

[0086] In a particularly preferred embodiment in this regard, the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazo-lin-4(3H)-one added to the solvent is the amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quina-zolin-4(3H)-one. In a further particularly preferred embodiment, the solvent is ethanol and is used to form a solution of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one.

[0087] In still another preferred embodiment, the present subject matter relates to a process for preparing a crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising:

- Dissolving (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one in a solvent selected from the group consisting of ethanol, ethyl acetate, dichloromethane, and a combination of ethanol and ethyl acetate to form a solution;
- Crystallizing crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one; and
- Drying said crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one.

[0088] In a preferred embodiment, the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one added to the solvent is the amorphous form of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. Further in this regard, the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one in the solvent is preferably first filtered and then heated to about 65° C to about 75° C in a vacuum to reduce the solvent content. In a preferred embodiment, the (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quin-azolin-4(3H)-one in the solvent is heated to about 70° C. And again, the most preferred solvent used in this regard is ethanol.

[0089] In an alternative embodiment, this process further comprises the step of refluxing the solution before crystallizing Form III. In a further alternative embodiment, this process comprises the additional step of filtering the solution after it is refluxed.

[0090] In a further preferred embodiment, the present subject matter relates to a process for preparing a crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one comprising:

- Adding (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one to an ethanol solvent to form a solution or suspension;
- Crystallizing crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one; and
- Drying said crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one.

Dosage

[0091] Appropriate dosage levels for the crystalline form of any of the active ingredients and/or their specific crystal forms are well known to those of ordinary skill in the art and are selected to maximize the treatment of the previously described microbial and/or fungal conditions. Dosage levels on the order of about 0.001 mg to about 5,000 mg per kilogram body weight of the active ingredient components are known to be useful in the treatment of the diseases, disorders, and conditions contemplated herein. Typically, this effective amount of the active agent will generally comprise from about 0.001 mg to about 100 mg per kilogram of patient body weight per day. Moreover, it will be understood that this dosage of ingredients can be administered in a single or multiple dosage units to provide the desired therapeutic effect.

[0092] If desired, other therapeutic agents can be employed in conjunction with those provided in the above-described compositions. The amount of pharmaceutically active

ingredients that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the nature of the disease, disorder, or condition, and the nature of the active ingredients.

[0093] The preferred pharmaceutical compositions may be given in a single or multiple doses daily. In a preferred embodiment, the pharmaceutical compositions are given from one to three times daily. Starting with a low dose twice daily and slowly working up to higher doses if needed is a preferred strategy. The amount of pharmaceutically active ingredients that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the nature of the disease, disorder, or condition, and the nature of the active ingredients.

[0094] It is understood, however, that a specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific pharmaceutically active agent; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; possible drug combinations; the severity of the particular condition being treated; and the form of administration. One of ordinary skill in the art would appreciate the variability of such factors and would be able to establish specific dose levels using no more than routine experimentation.

[0095] The optimal pharmaceutical formulations will be determined by one skilled in the art depending upon considerations such as the particular pharmaceutically active agent combination and the desired dosage. See, for example, "Remington's Pharmaceutical Sciences", 18th ed. (1990, Mack Publishing Co., Easton, PA 18042), pp. 1435-1712. Such formulations may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the essential lipids.

EXAMPLES

[0096] The presently presented compounds can be prepared in accordance with the following Examples using commercially available starting materials. The (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-tria-zol-1-yl)propyl]quinazolin-4(3H)-one used in the foregoing examples may be obtained by any of the currently available processes that are well known in the art, such as, for example, the processes described in Bartroli et al., J. Med. Chem., Vol. 41, No. 11, pp. 1869-1882 (1998). In solution, no crystalline form exists, and thus the physicochemical solution characteristics, i.e. 1H NMR spectra, ultraviolet spectra, and specific rotations of the crystalline and amorphous forms of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one are the same.

EXAMPLE 1

Preparation of crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one

[0097] Amorphous (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one was dissolved in ethanol and recrystallized. The original ^{1}H NMR spectrum showed about ½ mol of ethanol. The sample was kept in a capped vial at room temperature for 7 years. After 7 years, the samples NMR spectrum showed a total loss of ethanol. The sample was then shown to have crystalline Form III.

EXAMPLE 2

[0098] The procedure of Example 1 was repeated but substituting the ethanol with ethanol and ethyl acetate, ethyl acetate, or dichloromethane. In each case, the recrystallized sample was shown to have crystalline Form III.

EXAMPLE 3

Preparation of crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one

[0099] 6.785 kg of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one was dissolved in 17.3 L of ethanol. The solution was cooled at 10-20°C for about 2 hours. The obtained product was centrifuged and dried in vacuum at 70°C to obtain 5.796 kg of crystalline (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one. The product was then shown to have crystalline Form III.

EXAMPLE 4

Preparation of crystalline Form III of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-one

[0100] (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one was dissolved in an excess of hot ethanol. Charcoal was added and the solution was filtered. The filtered solution was then concentrated in vacuum to a final

volume of 2.5-3 L/kg of (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazo-lin-4(3H)-one. The concentrated solution was then cooled to 5-10°C and (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triaz-ol-1-yl)propyl]quinazolin-4(3H)-one crystallized. The obtained product was filtered and dried in vacuum at 70°C to obtain crystalline (1R,2R)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazo-lin-4(3H)-one. The product was then shown to have crystalline Form III.

EXAMPLE 5

[0101] A patient is suffering from onychomycosis. A preferred composition herein is administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 6

[0102] A patient is suffering from Chagas Disease. A preferred composition herein is administered to the patient. It would be expected that the patient would improve his/her condition or recover.

[0103] The present subject matter being thus described, it will be apparent that the same may be modified or varied in many ways. Such modifications and variations are not to be regarded as a departure from the spirit and scope of the present subject matter, and all such modifications and variations are intended to be included within the scope of the following claims.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US5807854A [0002]
- EP1282084A2 [0004]

Non-patent literature cited in the description

- **BARTROLI et al.**J. Med. Chem., 1998, vol. 41, 1869-1882 [0005]
- **SORBERA et al.**Drugs of the Future, 2003, vol. 28, 6529-537 [0006]
- **CAIRA**Topics in Current ChemistrySpringer Verlag Berlin Heidel-berg19980000vol. 198, [0007]
- **Z. OTWINOWSKIW. MINOR**Methods Enzymol., 1997, vol. 276, 307- [0053] [0055] [0056]
- XPREP in SHELXTL version 6.12Bruker AXS Inc.20020000 [0053]
- **M. C. BURLAR. CALIANDROM. CAMALLIB. CARROZZINIG. L. CASCARANOL. DE CARO, C. GIACO-VAZZOG. POLIDORIR. SPAGNA.**J. Appl. Cryst., 2005, vol. 38, 381- [0057]
- International Tables for CrystallographyInternational Tables for CrystallographyKluwer Academic Publishers19920000vol. C, [0059]
- **H. D. FLACK**cta Cryst., 1983, vol. A39, 876- [0060]
- A Program for Crystal Structure Refinement**G. M. SHELDRICK**SHELXL97Univ. of Gottingen19970000 [0061]
- **C. K. JOHNSON**ORTEPII, Report ORNL-5138Oak Ridge National Laboratory19760000 [0061]
- Mercury 1.4.1Cambridge Crystallographic Diffraction Center20050000 [0061]
- **J. GLUSKERK. TRUEBLOOD**Crystal Structure Analysis: A PrimerOxford University press1985000087- [0062]
- **BUDAVARI et al.**The Merck IndexMerck & Co., Inc.20010000 [0068]
- International Cosmetic Ingredient Dictionary and Handbook20040000 [0068]
- Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of ManagementInactive Ingredient Guide, [0068]
- **GILMAN et al.**Goodman and Gillman's: The Pharmacological Bases of TherapeuticsPergamon Press19900000 [0069]
- Remington's Pharmaceutical SciencesMack Publishing Co.19900000 [0069]
- Remington's Pharmaceutical SciencesMack Publishing Co.199000001435-1712 [0095]
- **BARTROLI et al.**J. Med. Chem., 1998, vol. 41, 111869-1882 [0096]

PATENTKRAV

1. Krystallinsk form af (1R,2R)-7-chlor-3-[2-(2,4-difluorphenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-on, som er Form III, hvori Form III har mindst en egenskab valgt fra gruppen bestående af:

et karakteristisk røntgenpulverdiffraktions(XRPD)mønster omfattende 2-theta-positioner ved 4,08, 5,73, 6,22, 7,77, 8,15, 8,80, 11,25, 11,47, 12,44, 13,09, 15,57, 17,63, 18,66, 20,85, 26,65 og 27,12 +/- 0,2;
og

et differentialscanningskalorimetri-termogram, som udviser en endoterm ved 105°C og har en onset-temperatur ved 99°C ± 5°C.

2. Krystallinsk form ifølge krav 1, hvori Form III har et mønster for infrarødt spektrum omfattende spektrallinjer ved 1677,0, 1600,0, 1557,5, 1498,3, 1462,6, 1403,0, 1318,4, 1272,5, 1254,1, 1170,0, 1138,7, 1101,6, 1060,2, 1016,4, 966,7, 932,7, 902,4, 855,5, 801,5, 785,8, 694,0, 677,9, 665,4, 631,7, 532,7 og 411,6 cm^{-1}.

3. Krystallinsk form ifølge krav 1, hvori Form III har et karakteristisk røntgenpulverdiffraktions(XRPD)mønster omfattende 2-theta-positioner ved 4,08, 5,73, 6,22, 7,77, 8,15, 8,80, 11,25, 11,47, 12,44, 13,09, 14,33, 14,68, 14,89, 15,57, 16,35, 16,68, 17,27, 17,63, 18,66, 19,32, 20,85, 22,12, 22,49, 23,58, 24,63, 25,02, 26,65, 27,12, 28,74, 29,11, 29,81, 31,35 og 33,48 +/- 0,2.

4. Krystallinsk form ifølge et af kravene 1 til 3, som har mindre end 10 vægt% af en anden krystallinsk form eller en amorf form af (1R,2R)-7-chlor-3-[2-(2,4-di-fluorphenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-on som bestemt på en vægt%basis.

5. Krystallinsk form ifølge et hvilket som helst af kravene 1-4, hvori den krystallinske form har mindst 90% renhed som defineret ved røntgenpulverdiffraktion.

6. Krystallinsk form ifølge et hvilket som helst af kravene 1-5, som har mindre end 10 vægt% af en hvilket som helst opløsningsmiddelrest.

7. Farmaceutisk sammensætning omfattende en anti-mikrobielt eller anti-fungalt effektiv mængde af den krystallinske form af (1R,2R)-7-chlor-3-[2-(2,4-difluorphenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-on ifølge et hvilket som helst af kravene 1-5 og en farmaceutisk acceptabel bærer.

8. Krystallinsk form af (1R,2R)-7-chlor-3-[2-(2,4-difluorphenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]quinazolin-4(3H)-on ifølge et hvilket som helst af kravene 1-7 til anvendelse til behandling og/eller forebyggelse af en mikrobiel infektion eller en svampeinfektion og/eller Chagas sygdom i et pattedyr.

DRAWINGS

Fig.1

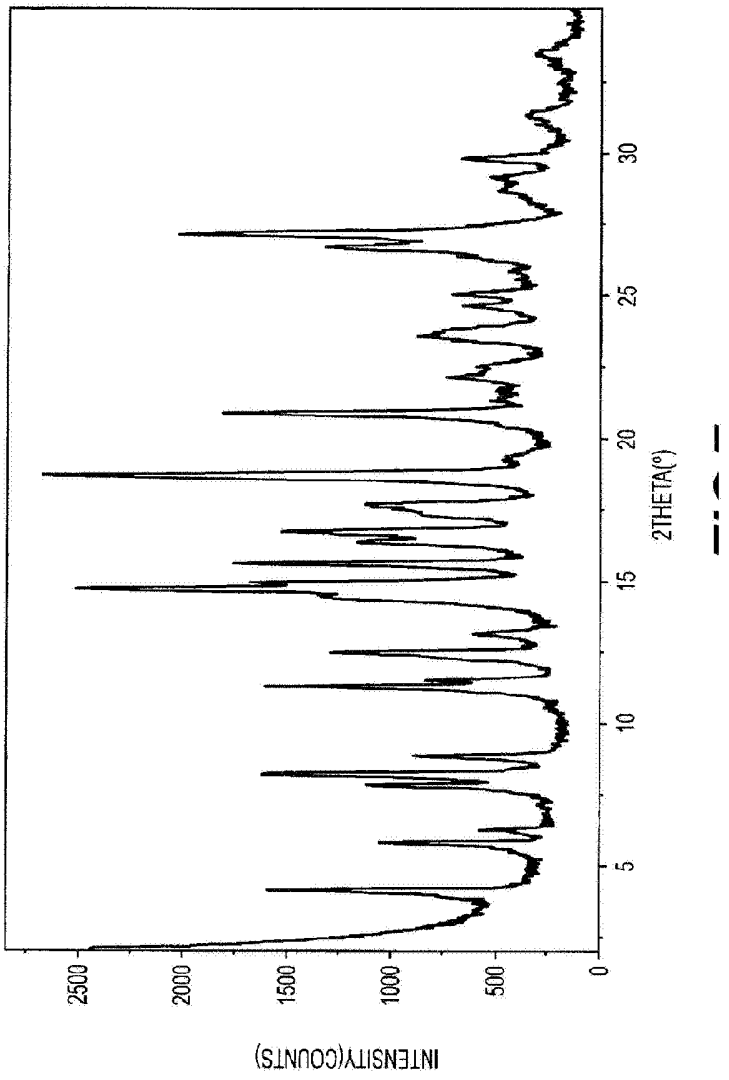


Fig.2

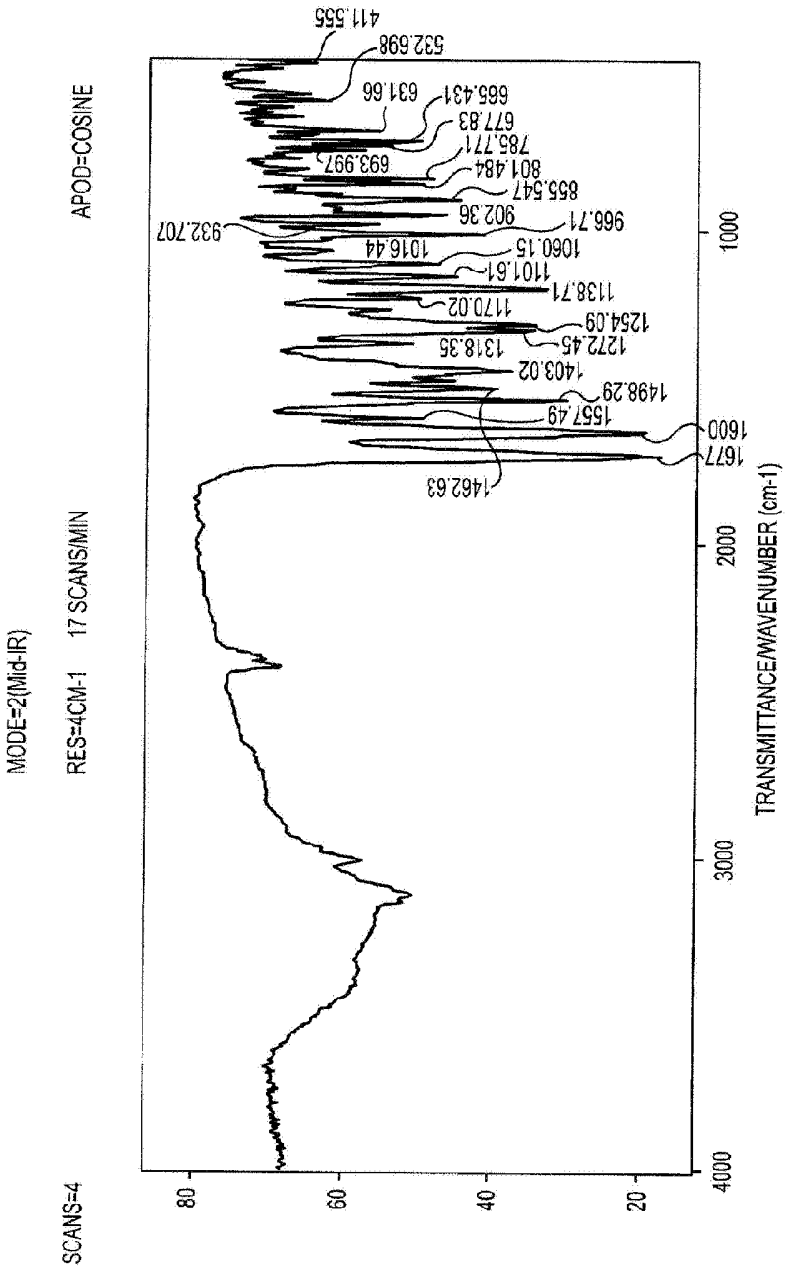

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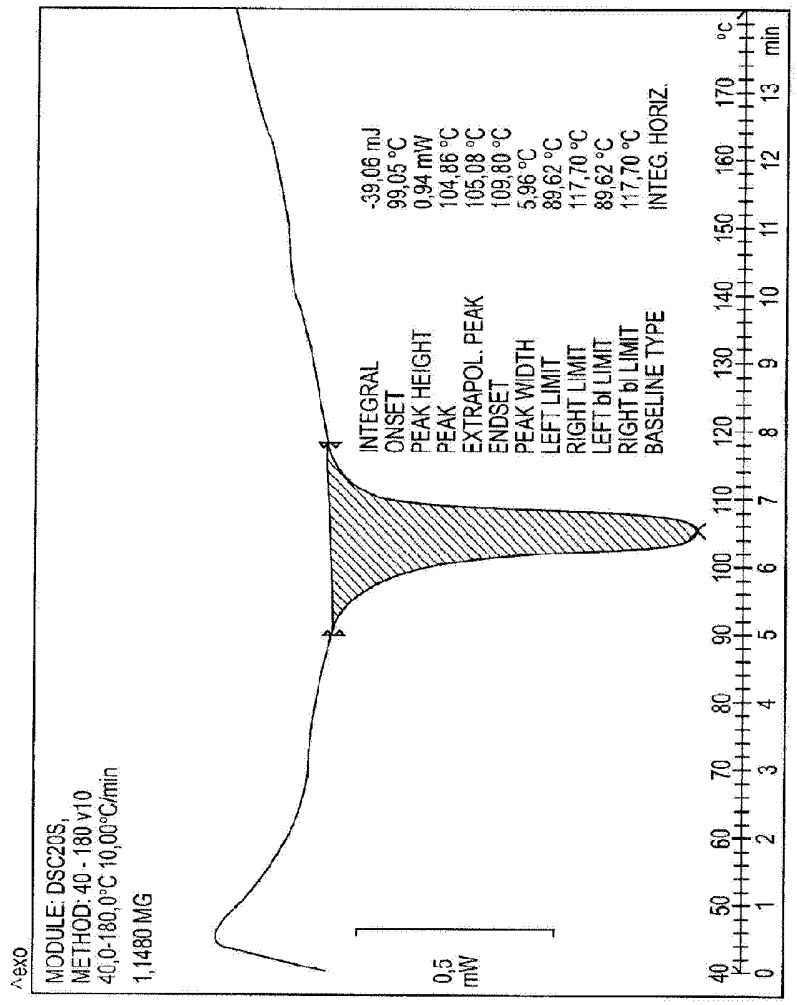
Fig.3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ENDSET 109,80 °C
PEAK WIDTH 5,96 °C
LEFT LIMIT 89,62 °C
RIGHT LIMIT 117,70 °C
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RIGHT bl LIMIT 117,70 °C
BASELINE TYPE INTEG. HORIZ.
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