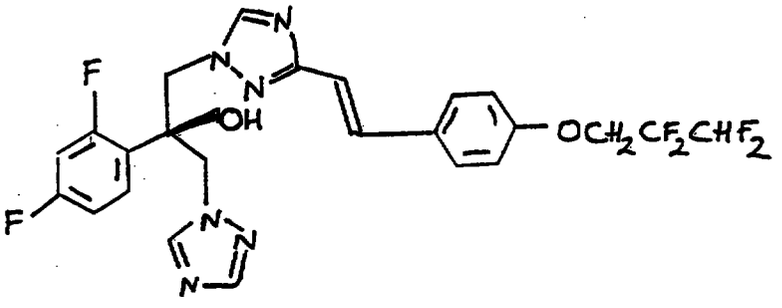
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CRYSTALLINE FORM OF AN ANTIFUNGAL AZOLE

The present invention relates to a novel crystalline form of a pharmaceutical compound, to processes for the preparation thereof, to pharmaceutical compositions comprising said crystalline form and to the use thereof in therapy.

European Patent Application Publication No. 472392 discloses the compound (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol as a very potent antifungal agent having a broad spectrum of activity. In particular this compound shows good activity against Candida albicans, Cryptococcus neoformans and Aspergillus fumigatus. The compound is known in the literature by the code D0870 (more recently ZD0870) and has the structure of formula (I):



(I)

Representative references in the literature to the antifungal activity of D0870 include Yamada et al., Antimicrobial Agents and Chemotherapy 1993; 37(11): 2412-7; Mochizuki et al., Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), New Orleans, 1993, 188 Abs. 377 and Edwards et al., Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), New Orleans, 1993, 80 Abs. 143.

EPA 472392 discloses that D0870 can be made into a variety of drug forms and mention is made of various types of formulation including tablets, capsules, granules, microgranules, powders, suppositories, syrups, emulsions, suspensions, aqueous and non-aqueous injectables.

This Sheet Has Been Replaced

In a preferred aspect it is desired to administer D0870 to patients in need thereof by way of an oral formulation, for example by a tablet formulation.

The present inventors have discovered that D0870 may be obtained as a solid in several different forms (both anhydrous and hydrated) each having distinct physical properties. Herein these different forms are referred to as Type I, Type II Polymorph, etc. wherein polymorphs refer to different crystalline forms of one compound. The distinctive physical properties of the different Types and Polymorphs may influence markedly the chemical and pharmaceutical processing of the compound, particularly on the industrial scale.

Examples 16 and 19 of EPA 472392 provide the compound of the formula (I) as crystals having a melting-point of 92-93.4°C and an infra-red spectrum (KBr pellet) recorded as 3130, 1618, 1606, 1515, 1500 and 1114cm^{-1}. These crystals are referred to hereinafter as Type II Polymorph.

Type II Polymorph has been studied on a relatively large scale and has been found to present problems, particularly in relation to stability which is regarded as of particular importance when considering the suitability of material for both bulk drug storage and for tablets manufacture.

It should be noted that D0870 contains a carbon-carbon double bond which is in the (E) [alternatively denoted as 'trans'] configuration. We have found that when Type II Polymorph is exposed to light significant quantities of the corresponding (Z) [alternatively denoted as 'cis'] isomer are formed. This is clearly undesirable and Type II Polymorph is not regarded as suitable for storage, manufacturing and in particular for a tablet formulation.

In addition, we have found that under conditions of high humidity Type II Polymorph will hydrate to form another physical form referred to herein as Type I. Type I is a hydrate. In other words Type II Polymorph is hygroscopic. One consequence is that formulation processes comprising wet granulation conditions would be difficult to carry out with consistent results. A further consequence would be that the shelf life of the resultant tablets could be adversely affected. These further problems confirm that Type II Polymorph is not regarded

as suitable for a tablet formulation.

As stated above, we have discovered a number of types and polymorphs of the compound of the formula (I).

Type I, a hydrate, is produced from Type II Polymorph under conditions of high humidity. Type I itself is relatively unstable and will dehydrate at elevated temperatures to reform Type II Polymorph. Thus Type I is unacceptable for storage, manufacturing and in particular for tablet manufacture because of inherent instability and formation of Type II Polymorph which, itself, is unacceptable.

We have now discovered Type IV Polymorph which solves the problems associated with Type II Polymorph and with Type I.

When exposed to light, Type IV Polymorph forms minimal quantities of the corresponding (Z)-isomer, well within the limits of pharmaceutical acceptability. Thus the problem of photolytic instability has been solved.

Furthermore, Type IV Polymorph is stable to conditions of high humidity, thus solving the problem of hygroscopicity.

Thus Type IV Polymorph fulfils the requirements of a pure, crystalline product that is convenient to process on a large scale, has good filtration characteristics, and possesses the necessary chemical and stability properties demanded of a pharmaceutical product.

Accordingly the present invention provides a physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol which physical form has an X-ray diffraction pattern having peaks at 2θ = 6.45, 11.37, 17.07, 18.06, 18.42, 18.92, 19.28, 19.56, 20.39, 21.18, 21.61, 22.28, 23.44, 24.01, 25.27, 26.86, 29.10, 30.43 and 30.80°.

The X-ray diffraction data were obtained using Siemens D5000 or D500 equipment as described in more detail hereinafter. The person skilled in the art will appreciate that different equipment and/or different conditions may result in different data as mentioned hereinafter. It should also be realised that some peaks may not be detectable if the product is in a pharmaceutical formulation.

In another aspect the present invention provides a physical

form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol having a melting-point of about 125°C.

The melting point of about 125°C was determined using differential scanning calorimetry (DSC) using a Mettler TA4000 system, as is described in detail hereinafter, and having a standard deviation of ±2°C. The person skilled in the art will appreciate that alternative readings of the melting point may result from the use of other types of DSC equipment and/or the use of the Mettler system under conditions different to those described below.

In a preferred aspect the physical form of the present invention is defined by means of the X-ray diffraction data and by means of the melting-point data.

In another aspect the present invention provides a physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol which physical form has an infra-red spectrum (2% w/w dispersion in KBr) having peaks at 654, 678, 820, 827, 838, 848, 856, 966, 971, 977, 983, 1063, 1089, 1098, 1108, 1119, 1129, 1141, 1180, 1200, 1210, 1220, 1247, 1263, 1277, 1343, 1428, 1506, 1513, 1519, 1599, 1608, 1619 and 3123 cm^{-1}.

The infra-red data were obtained by Fourier-transform spectroscopy on a 2% weight/weight dispersion in KBr using the Drift sampling techniques over the frequency range 4000-400cm^{-1}.

In addition, there is the potential for Type IV Polymorph to be characterised, and/or distinguished from other physical forms, by means of other techniques for example solid state nuclear magnetic resonance.

It is preferred that the physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (Type IV Polymorph) is substantially free of other physical forms of the compound of the formula (I). Where reference is made in this specifcaton to Type IV Polymorph and to its use in pharmaceutical compositions, it means that suitably at least 75% of the compound of the formula (I) is in the form of Type IV Polymorph. Preferably at

least 85%, more preferably at least 90%, and particularly at least 95%, of the compound of the formula (I) is in the form of Type IV Polymorph.

In order to use Type IV Polymorph (as hereinbefore defined) for the therapeutic treatment of mammals including humans, in particular in treating fungal infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises Type IV Polymorph and a pharmaceutically acceptable carrier.

Type IV Polymorph can be formulated into solid or liquid forms for example tablets, capsules, granules, microgranules, powders, suppositories, syrups, inhalation drugs, soft ointments, emulsions, suspensions, liquids for eye-drops, aqueous or non-aqueous injectables, emulsion or suspension injectables, or solid injectables used by dissolving, emulsifying or suspending at the time of use.

Such formulations may be prepared by appropriate selective combination of excipients, binders, lubricants, colourants, flavourings, suspension agents or emulsifiers (for example polysorbate 80 or gum arabic), appropriate types of generally used carriers or solvents, for example sterile water as needed or vegetable oil, and also pharmaceutically acceptable solvents or solution aids (for example alcohol, glycerine or propylene glycol).

As stated hereinabove Type IV Polymorph is of particular benefit in the formulation of tablets and pharmaceutical formulations in tablet form are a particularly preferred aspect of the present invention.

Pharmaceutical compositions of the present invention may be adminstered to the patient either orally or parenterally (for example intravenously, intramuscularly, subcutaneously, intrarectally, by percutaneous absorption or transmucosal absorption), or by application in a pessary. In the case of tablets, capsules, powders, injectables, suppositories (systemic) or other systemic administrations, for the daily dosage, calculated in terms of the amount of the compound of the invention, typically administration of 0.1 mg - 2000 mg, preferably

1 mg - 200 mg, is desirable, and this can be appropriately varied depending on the condition of the patient. It is also possible to give the daily dosage at a single time, to divide it into 2-6 doses or to give it as an intravenous drip or similar.

The compound of the formula (I) shows an acceptable toxicity profile and this holds true for Type IV Polymorph.

Further details of the therapeutic use of the compound of the formula (I), which details appertain to the novel Type IV Polymorph, are to be found in the various references relating to D0870.

In another aspect the present invention provides a process for preparing Type IV Polymorph as hereinbefore defined which process comprises dissolving a source of the compound of the formula (I) in a C_{1-4}alkanol or mixture thereof, preferably ethanol, heating to an elevated temperature, diluting with water at a similar elevated temperature and allowing to cool.

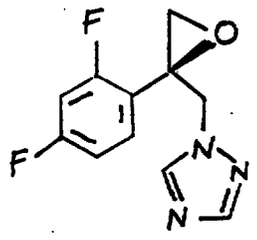
Conveniently on the large scale industrial methylated spirits are used and dissolution of the compound of the formula (I) is performed at ambient or slightly elevated temperature for example in the range 15 - 35°C such as about 30°C.

Typically the temperature of the solution is elevated to within a range 40 - 70°C for example in the range 50 - 60°C, and treated with water whilst maintaining an elevated temperature. Preferably the water is filtered and demineralised; typically about 5-7 parts by weight of water are added.

The resultant solution is either cooled or is allowed to cool slowly whereupon Type IV Polymorph is formed. This may be collected, washed and dried in conventional manner.

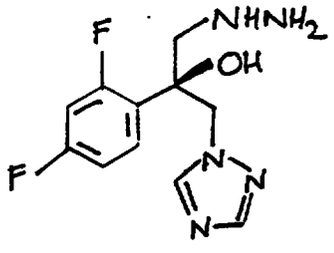
Conveniently the source of the compound of the formula (I) may be the product of either Example 16 or Example 19 of EPA 472392. In an alternative the compound of the formula (I) may be prepared by the following general method which comprises the steps of:

i) reacting a compound of the formula (C)



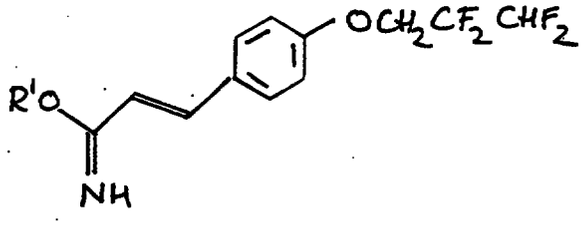
(C)

with hydrazine or a chemical equivalent thereof to form a compound of the formula (II):



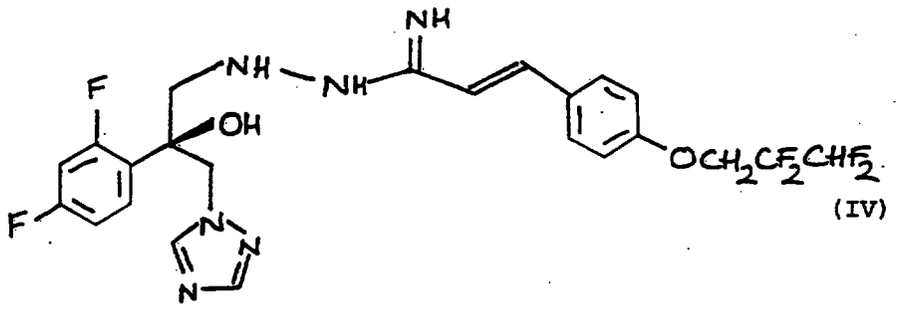
(II)

ii) reacting the compound of the formula (II) with an iminoether of the formula (III) or a chemical equivalent thereof:



(III)

wherein R^1 is C_{1-6}alkyl or optionally substituted phenyl; to form a compound of the formula (IV):



(IV)

iii) reacting the compound of the formula (IV) with a compound of the formula (V):

$$(R^2O)_3CH \qquad (V)$$

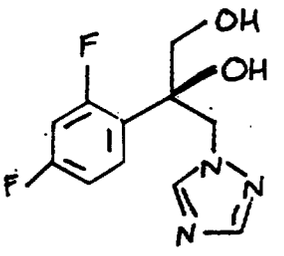
wherein R^2 is C_{1-6}alkyl or optionally substituted phenyl to form a compound of the formula (I).

The reaction of a compound of the formula (C) with hydrazine or a chemical equivalent thereof is performed under conditions conventional for the ring opening of epoxides. The reaction is typically performed in an organic solvent or mixture of solvents for example toluene or a C_{1-4}alkanol for example isopropanol or isobutanol. The reaction is performed at a non-extreme temperature such as between 0-60°C but is preferably performed at approximately ambient temperature for example 15-35°C, typically about 25°C. The reaction is typically performed in a substantially inert atmosphere for example under nitrogen at normal pressure.

Hydrazine or its chemical equivalent may be used in the reaction. Conveniently hydrazine is present as hydrazine hydrate.

The compound of the formula (C) is known from EPA 472392 wherein it is described in Example 15. It may be introduced into the process of the present invention as isolated material or it may be prepared and reacted in situ. For example it may be prepared from the

precursor diol of the formula (VI):



(VI)

and introduced into the process as a solution in toluene or similar solvent. This has been found to be advantageous as it avoids any difficulties associated with the handling of a solid compound of the formula (C).

The compound of the formula (II) may be isolated or may be prepared and used in situ, or in solution, in the next step of the process. Again, use in a solution has been found to be advantageous in order to avoid any difficulties associated with the handling of the solid compound of the formula (II).

The reaction of the compound of the formula (II) and an iminoether of the formula (III) or a chemical equivalent thereof is performed in a substantially inert organic solvent such as a hydrocarbon or C_{1-4}alkanol, preferably an alkanol and most preferably isobutanol. The reaction is performed at a non-extreme temperature such as between 0-60°C but is preferably performed at approximately ambient temperature for example 10-30°C.

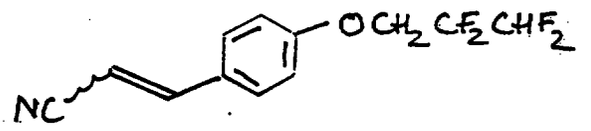
The reaction is typically performed in a substantially inert atmosphere for example under nitrogen at normal pressure.

The compound of the formula (IV) may be isolated in any convenient manner. A particular advantage is that it is crystalline. This enables easier isolation and purification of this key intermediate.

In the compound of the formula (III), R^1 is C_{1-6}alkyl or optionally substituted phenyl. Suitably R^1 is methyl, ethyl, propyl or butyl. Preferably R^1 is methyl.

The compounds of the formula (III) may be prepared by

reaction of a compound of the formula (VII):



(VII)

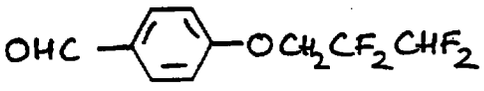
with a compound of the formula R^1OH wherein R^1 is as hereinbefore defined. Suitably R^1OH is methanol, ethanol, propanol or butanol. Preferably R^1OH is methanol.

The reaction between the compounds of the formula (VII) and R^1OH is generally performed in an organic solvent or a mixture of organic solvents. Conveniently the solvent, or one of the solvents, is the alcohol R^1OH in excess. A suitable co-solvent, if present, is a hydrocarbon for example toluene. The reaction is conveniently performed at a non-extreme temperature for example -10°C to +20°C, preferably at about 5°C.

It is necessary that the compound of the formula (III) is provided in the trans or (E)-configuration, as the final product of the formula (I) is in such configuration. Surprisingly we have found that it is not necessary to have the trans or (E)- cinnamonitrile of the formula (VII) in order to obtain the trans or (E)- compound of the formula (III). We have discovered that the compound of the formula (VII) may be in either cis- or trans -configuration; both compounds provide good conversion to the required trans- compound of the formula (III). This is a highly advantageous finding as it removes the necessity of separating cis and trans isomers of the compound of the formula (VII) prior to reaction with R^1OH.

The compounds of the formula (III) may be isolated or may be prepared and used in situ. Advantageously this is prepared as a partially purified solid and is reacted by dissolution in a solution of the compound of the formula (III).

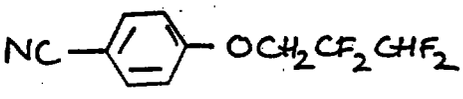
Conveniently the compounds of the formula (VII) may be prepared by reaction of a compound of the formula (VIII):



(VIII)

or a protected derivative thereof for example an acetal, with a source of CH_2CN. Suitably the source of the CH_2CN is a cyanomethyl-phosphonate for example diethylcyanomethylphosphonate. The reaction is performed in the presence of base. In one aspect the reaction is performed in an aqueous or aqueous-organic medium, the base is water soluble for example a carbonate such as potassium carbonate, and a phase-transfer agent is present to aid dissolution and reaction. The reaction is performed at a non-extreme temperature for example 10-60°C for example approximately 40°C.

Typically the compound of the formula (VIII) is formed and reacted in situ from the corresponding nitrile of the formula (IX):



(IX)

by methods conventional for converting nitriles to aldehydes, for example using nickel:aluminium alloy in the presence of acetic acid and heat, or using diisobutylaluminium hydride.

The compounds of the formulae (VIII) and (IX) are known from EPA 472392.

The reaction of the compound of the formula (IV) with a compound of the formula (V) is carried out in a substantially inert organic solvent such as a hydrocarbon for example toluene. The reaction generates an alkanol as a by-product and it is convenient to select a solvent that will form an azeotrope with said alkanol permitting ready removal by distillation. Accordingly the reaction is typically performed at a temperature sufficiently elevated to allow azeotropic distillation.

The compound of the formula (V) is suitably trimethyl

orthoformate or triethyl orthoformate. Preferably $(R^2O)_3CH$ is triethyl orthoformate.

The invention is now illustrated by means of the following Examples, data and Figures in which:

Figure 1 is the X-ray diffraction spectrum for Type IV Polymorph obtained using a Siemens D5000 machine in Θ - Θ configuration over the scan range 2° 2Θ to 34° 2Θ with 4 seconds exposure per 0.02° 2Θ increment.

The reflections are quoted as their centroid values (calculated by a computer package such as DIFFRAC/AT). The sample was prepared by micronisation to reduce the grain size and aspect ratio of the crystals and gentle trituration to break up crystal aggregates, followed by filling the sample into a standard holder (having a flat lip) and compressing flush to the lip with a glass microscope slide. It should be realised that analysis of samples with grains above 30 microns in size and non-unitary aspect ratios may affect intensity variations between peaks. Also the skilled person will realise that the position of reflections is affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect.

Figure 2 is the drift Fourier-transform infra-red spectrum recorded on a 2% sample of Type IV Polymorph in KBr using the drift sampling technique over the frequency range 4000-400cm^{-1}.

Figure 3 is the DSC graph for Type IV Polymorph obtained on a Mettler TA4000 system, consisting of a DSC measuring cell and TC11 control processor (calibrated with Indium). Sample weight was approximately 1 to 6 mg; the pan type was pierced aluminium; the atmosphere was nitrogen (100ml/min) and the temperature range studied was 50° - 150°C at a rate of 10°C/minute.

The skilled person will realise that the precise value of the

melting-point will be influenced by the purity of the compound, the sample weight, the heating rate and the particle size.

Figure 4 (for comparison) is the X-ray diffraction spectrum for Type II Polymorph obtained using a Siemens D5000 machine in Θ - Θ configuration over the scan range 2° 2Θ to 34° 2Θ with 4 seconds exposure per 0.02° 2Θ increment.

Figure 5 (for comparison) is the drift Fourier-transform infra-red spectrum recorded on a 2% sample of Type II Polymorph in KBr using the drift sampling technique over the frequency range 4000-400cm^{-1}.

COMPARATIVE TESTING OF TYPE II POLYMORPH AND TYPE IV POLYMORPH

Accelerated stability studies were performed on samples of Type II and Type IV Polymorphs stored for up to 28 days:

in sealed glass containers under the following conditions:

i) at 80°C and ambient humidity;

and in open glass containers under the following conditions:

ii) at 30°C and 90% relative humidity;
iii) in an open Petri dish stored in a light cabinet (5000 Lux)

RESULTS

Test	Time (days)	Analysis	
		II	IV
	0	100.1	100.0
i	7	99.6	100.3
	28	99.5	101.2
ii	7	98.2	101.8
	28	96.3	100.4
iii	7	92.7	101.3
	28	93.0	100.0

Analysis of Type II Polymorph or Type IV Polymorph by hplc (%w/w).

According to the above tests, after four weeks there was no significant change in the stability of the Type IV Polymorph with no interconversion to other forms. However, the Type II Polymorph had undergone significant decomposition in either relatively humid conditions or in the presence of light.

EXAMPLES

In the examples;

TW refers to the Twaddle specific gravity scale;
hplc means high performance liquid chromatography;
^{1}H nmr were recorded at 270MHz with shifts given in δ ppm.

EXAMPLE 1

(R)-2-(2,4-Difluorophenyl)-1-(3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)-styryl]-1H-1,2,4-triazol-1-yl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol

(i) (R)-2-(2,4-Difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol (51 g), p-toluenesulphonyl chloride (42 g) and tetrabutylammonium bromide (2 g) were charged to a reaction vessel. Toluene (400 ml) and water (90 ml) were added and the mixture was cooled to 16°C. Sodium hydroxide (27.3 ml; 100° TW) was added, with washing in with water (10 ml). The mixture was stirred vigorously for 1 hour and checked (by hplc) for completion of the reaction. Water (370 ml) was added and, after 20 minutes of stirring, the lower aqueous layer was separated. The interphase was run off with the aqueous layer. The aqueous layer was extracted with toluene, stirred for 15 minutes and allowed to settle for 15 minutes. The aqueous layer was separated retaining the interphase with the organic layer. The organic extracts were combined, stirred with water (100 ml) for 15 minutes, filtered through diatomaceous earth (1 g), washed through with toluene (25 ml) and separated.

The upper organic layer was distilled to about 100 ml volume at approximately 20 mmHg pressure with a bath temperature at a maximum of 40°C.

This procedure provided a solution of (R)-1-[2-(2,4-difluorophenyl)oxiran-2-ylmethyl]-1H-1,2,4-triazole [Compound (C)].

ii) Isobutanol (200 ml) was added to the solution of compound C (from i) above) at ambient temperature under nitrogen. Subsequently hydrazine hydrate (54 ml) was added, maintaining the temperature at 25°C, washing in with isobutanol (22 ml). The mixture was stirred for 3.5 hours and it was checked (by hplc) that the reaction was complete. The solution was washed with saturated brine (4 x 58 ml), stirring for 15-30 minutes and allowing to settle for 30 minutes after each wash.

This procedure provided a solution of 2-(2,4-difluorophenyl)-1-hydrazino-3-(1H-1,2,4-triazol-1-yl)propan-2-ol in isobutanol which was used without further isolation.

iii) To 4-(2,2,3,3-tetrafluoropropoxy)cinnamonitrile (44 g cinnamonitrile as ~20% w/v solution to toluene) was added methanol (76 ml) and the solution was cooled to 5°C. The reactor was evacuated, purged with nitrogen 3 times and then re-evacuated. Hydrogen chloride gas was introduced via a balloon, replenishing as necessary over 3 hours. The reaction was allowed to stir under an atmosphere of hydrogen chloride for 16 hours at ambient temperature. Toluene (176 ml) was added and the reaction mixture set for distillation under water pump vacuum with the bath temperature set at 35°C and distillation was continued to a batch temperature of 25°C at 70 mBar.

Ethyl acetate (88 ml) was added, the suspension stirred at 30°C for 30 minutes and then cooled to 5°C for 30 minutes. The solid was collected on an enclosed filter, washed with cold toluene (50 ml) and dried. The methyl (E)-4-(2,2,3,3-tetrafluoropropoxy)cinnamimidate hydrochloride product was held on the filter for reaction in part iv) below; ^{1}H nmr (DMSO-d_6): 4.12 (s, 3H); 4.70 (t, 2H); 6.97 (m, 2H); 7.18 (d, 2H); 7.72 (d, 2H); 7.95 (d, 1H); 11.60 (broad s, 1H).

iv) The hydrazino alcohol solution from part ii) above was added to the cinnamimidate from part iii) above agitating the mixture on the filter until the solid had dissolved (30-60 minutes). The solution was transferred to the reaction vessel and washed through with isobutanol (30 ml). The reaction mixture was stirred for 3 hours

under nitrogen and checked for the end of reaction by hplc. A solution of sodium carbonate (19.2 g) in water (260 ml) was added, the batch was stirred for 10 minutes and then separated. The upper organic layer was stirred with water (100 ml) and methyl tert-butyl ether (100 ml) for 30 minutes and then separated.

The upper organic layer was distilled to a volume of ~150 ml under vacuum (water pump), at a maximum bath temperature of 35°C giving a final batch temperature of 28°C at ~20 mBar.

Xylene (360 ml) was added and the mixture redistilled under vacuum to a volume of approximately 250 ml with a jacket temperature of 40°C and pressure of ~20 mBar. Cyclohexane (100 ml) was added and the mixture held at 40°C for 30 minutes before cooling to 20°C over 2 hours and to 5°C for 2 hours.

The product was separated by filtration and washed with 1:1 xylene/cyclohexane (80 ml) then cyclohexane (40 ml). The product was dried in a vacuum oven at 45°C to give (E)-N-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]-4-(2,2,3,3-tetrafluoropropoxy)cinnamamidrazone (56.26 g); ^{1}H nmr (DMSO-d_6): 3.40 (m, 2H); 4.60 (m, 4H); 5.20 (broad s, 1H); 5.65 (broad s, 2H); 6.30 (d, 1H); 6.60-7.45 (m, 10H); 7.72 (s, 1H); 8.30 (s, 1H); m.p. 137-140°C.

v) The above product (52.8 g) was suspended in toluene (285 ml) and agitated at ambient temperature. To this suspension was added triethylorthoformate (17.82 g). The mixture was heated to 100°C for 2-3 hours allowing the ethanol/toluene azeotrope to be removed by distillation.

The reaction mixture was cooled to 60°C and cyclohexane (65 ml) was added. The reaction mixture was further cooled to 50°C for 30 minutes to establish crystallisation whereupon cyclohexane (150 ml) was added. The suspension was cooled to 20°C over 2 hours and cooled to 5°C for a further hour. The product was collected by filtration, washed with (1:1) toluene/cyclohexane (90 ml), washed with cyclohexane (50 ml) and

dried in vacuo at 45°C to give the title compound (52.5 g).

This compound (1 part by weight) may be purified in the following manner:

a) suspension in methyl t-butyl ether (10 parts by weight);
b) heating under reflux for 30 minutes to dissolve the solid;
c) cooling to 25°C over 1 hour;
d) cooling to 5°C for 2 hours;
e) collecting product by filtration;
f) washing with methyl t-butyl ether (2 x 1.5 parts by weight);
g) drying in vacuo at 45°C.

and may be further purified as follows:

h) charging compound and pulverised carbon (0.1 parts by weight) to a reactor with industrial methylated spirit (IMS) (5 parts by weight);
i) heating to 55°C;
j) holding the mixture for 60 minutes;
k) filtering at 50°C washing through with IMS (1 part by weight);
l) heating to 60°C with the addition of demineralised water (6 parts by weight);
m) seeding the solution (with material previously obtained), holding it at 60°C overnight;
n) programmed temperature recycling followed by cooling to 10°C;
o) collecting product by filtration, washing through with demineralised water (4 parts by weight);
p) drying to constant weight with hot nitrogen at 45°C;
to give Type IV Polymorph with a melting point of about 125°C and X-ray diffraction and infra-red spectra as shown in Figures 1 and 2;
^{1}H nmr ($CDCl_3$): 4.25-4.90 (m, 6H); 5.59 (s, 1H); 6.08 (tt, 1H); 6.70-7.00 (m, 5H); 7.35-7.65 (m, 4H); 7.88-8.11 (s, d, 3H);
$[\alpha]_D^{20}$ = +23±2 (c = 1.0 in methanol).

EXAMPLE 2

Preparation of 4-(2,2,3,3-tetrafluoropropoxy)cinnamonitrile used in Example 1 iii).

4-(2,2,3,3-Tetrafluoropropoxy)benzonitrile (100.0 g) and 1:1 nickel:aluminium alloy (50.2 g) were agitated in water (215 ml) and the mixture heated to reflux before adding 80% acetic acid (846 ml) over a period of 1 hour. Once the addition was over, agitation and heating were maintained until hplc analysis indicated that the reaction was complete. The mixture was cooled to 80°C and filtered through diatomaceous earth which was blown fairly dry and washed with water (129 ml), toluene (600 ml), and water (248 ml). The aqueous phase was separated off, extracted with toluene (143 ml), and the combined toluene extracts washed twice with water (2 x 143 ml) then once with a solution of potassium carbonate (14.3 gms) in water (143 mls) to produce 4-(2,2,3,3-tetrafluoropropoxy)- benzaldehyde; ^{1}H nmr ($CDCl_3$): 4.45 (t, 2H); 6.10 (tt, 1H); 7.05 (d, 2H); 7.90 (d, 2H); 9.95 (s, 1H).

To the agitated solution of aldehyde was added water (286 ml), Aliquat 336 (7.0 g) and potassium carbonate (63.7 g). Diethylcyanomethyl- phosphonate (1.05 equivalents based on aldehyde content) was added and the contents temperature raised to 40°C. When HPLC analysis indicated end of reaction the two phases were allowed to settle, the lower aqueous phase separated and the toluene solution washed with 15% brine (235 ml). The volume of the toluene solution was reduced from around (740 ml) to 488 ml by atmospheric distillation to give an approximately 20:80 mixture of cis- and trans-isomers; ^{1}H nmr (DMSO-d_6): cis-isomer; 4.70 (t, 2H); 5.75 (d, 1H); 6.70 (tt, 1H); 7.20 (d, 2H); 7.35 (d, 1H); 7.85 (d, 2H): trans-isomer: 4.67 (t, 2H); 6.20 (d, 1H); 6.53 (tt, 1H); 7.15 (d, 2H); 7.55 (d, 1H); 7.70 (d, 2H).

EXAMPLE 3

A tablet formulation is prepared as follows:

Ingredients

Type IV Polymorph	10 mg
microcrystalline cellulose	149 mg
pre-gelatinised starch	25 mg
polyvinylpyrrolidine	4 mg
sodium starch glycollate	10 mg
magnesium stearate	2 mg

Type IV Polymorph (10 mg), microcrystalline cellulose (149 mg), pre-gelatinised starch (25 mg) and polyvinylpyrrolidine (4 mg) are mixed together with water. The dried granules are blended with sodium starch glycollate (10 mg) and magnesium stearate (2 mg).

The tablets are film coated with a coating of hydroxypropylmethyl cellulose 2910 (5 mg), Macrogol 6000 (0.5 mg) and titanium oxide (1 mg).

Tablets containing 25 mg and 100 mg Type IV Polymorph may be obtained in a similar manner with a concomitant reduction in the microcrystalline cellulose content.

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CLAIMS

1. A physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol which physical form has an X-ray diffraction pattern having peaks at 2θ = 6.45, 11.37, 17.07, 18.06, 18.42, 18.92, 19.28, 19.56, 20.39, 21.18, 21.61, 22.28, 23.44, 24.01, 25.27, 26.86, 29.10, 30.43 and 30.80°.

2. A physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol which has a melting-point of about 125°C.

3. A physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol which physical form has an X-ray diffraction pattern having peaks at 2θ = 6.45, 11.37, 17.07, 18.06, 18.42, 18.92, 19.28, 19.56, 20.39, 21.18, 21.61, 22.28, 23.44, 24.01, 25.27, 26.86, 29.10, 30.43 and 30.80° and a melting-point of about 125°C.

4. A physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol according to any one of claims 1-3 which has an infra-red spectrum (2% w/w dispersion in KBr) having peaks at 654, 678, 820, 827, 838, 848, 856, 966, 971, 977, 983, 1063, 1089, 1098, 1108, 1119, 1129, 1141, 1180, 1200, 1210, 1220, 1247, 1263, 1277, 1343, 1428, 1506, 1513, 1519, 1599, 1608, 1619 and 3123 cm^{-1}.

5. A physical form of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol according to any one of claims 1-4 substantially free of other physical forms of the said compound.

6. A physical form according to claim 5 when at least 90% free of other physical forms.

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* C L M S *

7. A pharmaceutical composition in solid form comprising a physical form according to any one of claims 1-6 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to claim 7 in the form of a tablet.

9. A pharmaceutical composition for reconstitution as an injectable solution, emulsion or suspension which comprises a physical form according to any one of claims 1-6 and a suspension agent, emulsifier or solvent.

10. A pharmaceutical composition in liquid form prepared by dissolution of a physical form according to any one of claims 1-6.

11. A process for preparing a physical form according to any one of claims 1-6 which comprises dissolving a source of (+)-2-(2,4-difluorophenyl)-1-[3-[(E)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1H-1,2,4-triazol-1-yl]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol in a C_{1-4}alkanol or mixture thereof, heating to an elevated temperature, diluting with water and allowing to cool.

12. A physical form according to anyone of claims 1-6 for use in a method of treatment of therapy.

13. The use of a physical form according to any one of claims 1-6 for the manufacture of a medicament for the treatment of fungal infection.

14. A method of treating a patient in need thereof with an antifungally effective amount of a physical form according to any one of claims 1-6.

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