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(56) Documents Cited:
WO 1993/007139 A1 **CN 001919846 A**
CN 001473825 A
Zhongguo Yiyao Gongye Zazhi, 2005, Vol.36(10), Wang et al., pp.653-655.
Organic Process Research & Development, 2001, Vol.5(1), Butters et al., pp.28-36.

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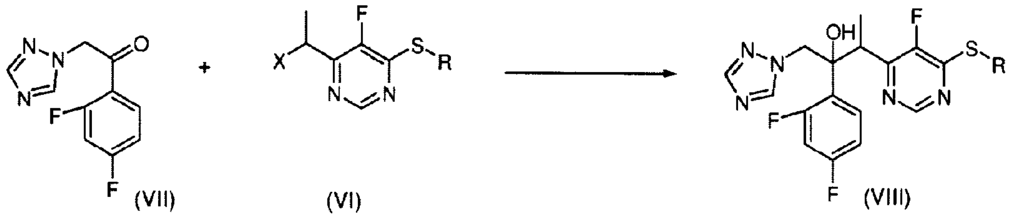
(54) Abstract Title: **Process for the preparation of voriconazole**

(57) A process for the preparation of voriconazole is described wherein sulfide substituted pyrimidines are key intermediates. The sulfide substituents render the pyrimidines particularly suitable for metal mediated addition to ketones. The key reaction step, which is preferably zinc-mediated, involves the preparation of a compound of formula (VIII) by a cross-coupling reaction of a compound of formula (VII) and a compound of formula (VI):



wherein R is C_{1-12}alkyl, C_{2-12}alkenyl, C_{1-3}alkylaryl, aryl, heterocyclic, C_{1-3}alkylheterocyclic, C_{1-12}alkyl substituted by alkoxy, C_{1-12}alkylthio, C_{1-12}alkylamino, C_{1-12}dialkylamino, COC_{1-12}alkyl, aryl, aryloxy or an O-C_{1-6} alkylaryl group wherein any aryl group may be substituted with 1-3 groups selected from Cl, Br, F, Me, OEt, OMe, methyl or ethyl; and X is a leaving group, preferably Br. Voriconazole (IX) may be prepared from (VIII) by a Raney nickel reduction to remove the thioether. The preparation of (IX) from thiol precursor (IV) is also outlined. The intermediates are also claimed per se.

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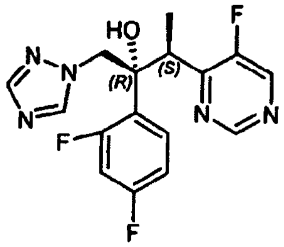
Process For Pharmaceutical Compound

The present invention relates to an improved process for the preparation of voriconazole and to intermediates useful in that process. Voriconazole is (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol and is represented by Formula I:



Formula (I)

Voriconazole is a chiral antifungal agent belonging to the class of triazole antifungals. The drug is indicated for the treatment of invasive aspergillosis (*Aspergillus fumigatus*) and esophageal candidiasis (*Candida albicans*), as well as infections caused by *Scedosporium apiospermum* and *Fusarium* spp.

Voriconazole falls within the general structures within EP 0 357 241 A1. However, the first document specifically describing the preparation of voriconazole is EP 0 440 372 A1. The process described therein included the reaction of 4-chloro-6-ethyl-5-fluoropyrimidine with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone in the presence of a strong base under cryogenic conditions. The coupling product was isolated by chromatography in 12% yield as the wanted (2R,3S/2S,3R)-enantiomeric pair. The chloro-substituent in the intermediate pyrimidine was removed by hydrogenolysis and the product isolated after chromatography. The racemate was resolved by crystallisation with R-(-)-10-camphorsulfonic acid followed by basification and crystallisation of voriconazole as the free base. The synthesis potentially suffers from several disadvantages in scale-up and manufacturing work. The preparation gave a low diastereoselectivity and provided the desired product in a low chemical yield. Furthermore, separation of the enantiomeric pairs was by costly chromatographic methods. Hence, improvements of the voriconazole synthesis were needed.

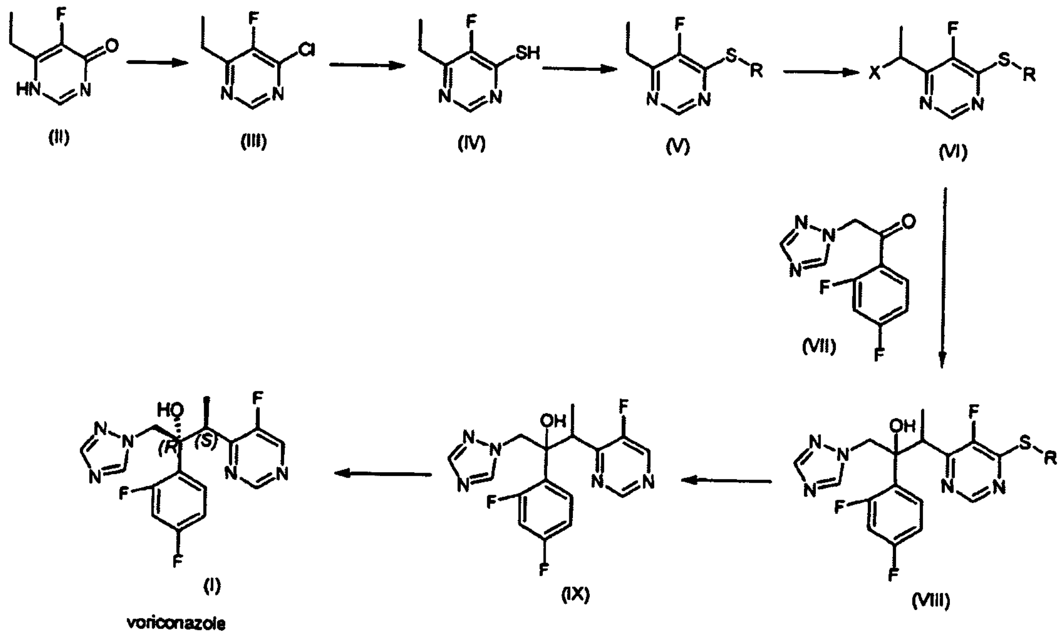
US 6,586,594 B1 discloses an improved coupling step in the synthesis of voriconazole. In the original process the ethyl side-chain in the pyrimidine was deprotonated by treatment with a strong base for the coupling reaction. The coupling partner is an α-bromoethylpyrimidine which was zincated by activated zinc metal. In this way the US 6,586,594 B1 allowed cryogenic conditions employed in EP 0 440 372 A1 to be avoided. The diastereoselectivity was increased to about 9 : 1 in favor of the desired (2R,3S/2S,3R) enantiomeric pair over the (2R,3R/2S,3S) enantiomeric counterpart. The chemical yield was about 65%. However, the process suffered from partial dimerisation of the electrophilic pyrimidine substrate resulting in an unwanted consumption of starting material besides formation of other unwanted byproducts (described in more detail in Butters *et al.*, *Org. Proc. Res. Dev.* **2001**, *5*, 28-36).

WO 2006/065726 A2 claims a polymorphic form A as well as amorphous voriconazole. It was shown that polymorphic form B of voriconazole was obtained in earlier disclosures. The patent application suggests voriconazole of a purity more than 95%, 99% and 99.5% by HPLC can be obtained, but no HPLC conditions were given. A process for the production of voriconazole was also disclosed.

In WO 2007/013096 A1, a further process is disclosed for the production of voriconazole. The process is similar to that of EP 0 440 372 A1 and uses a strong base under cryogenic conditions. Small improvements over the original process were reported.

Clearly an improved process for the preparation of voriconazole is still required.

The present invention relates to a new process for production of voriconazole. A key step in this process is the coupling of a 4-(1-halogenoethyl)-5-fluoro-6-thiopyrimidine derivative (VI) or analogue with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (VII), (see Scheme I). It has been found that in this way unwanted side-reactions are avoided, or greatly reduced, possibly because the substituted thio group renders the pyrimidine ring less electrophilic than its 6-chloro analogue. The incorporation of the substituted thio group has also been found to lead to usefully modified chemical reactivities and physicochemical properties, possibly because of increased electron density in the pyrimidine ring.



Scheme I.

It has been realized that most of the difficulties reported for the coupling of the zincated pyrimidines with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (VII) can be overcome by using pyrimidine substrates carrying electron donating-SR substituents. This particular electron donating substituent can readily be removed at a later stage in the overall synthesis of the final target compound. The new substrates of the invention are pyrimidine-4(6)-sulfides such as (VIII), (VI), (V) and (IV).

The positive effect of the electron donating substituents is illustrated by the coupling of 4-(1-bromoethyl)-5-fluoro-6-(methylthio)pyrimidine with 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (VII). The desired product, compound of Formula (VIII) (R=methyl), was isolated in 79% yield, which is a considerable improvement from 65% yield reported in US 6,586,594 B1.

The useful intermediate 6-ethyl-5-fluoropyrimidine-4-thiol (of the formula IV in Scheme I) can be prepared as described in Example 1 and 2 herein.

The group R in compounds shown in Scheme I, may be any suitable moiety other than H such that SR increases the electron density on the pyrimidine ring and which is removable by reduction.

Aptly R may be an alkyl, alkenyl, alkylaryl, aryl, alkylheteroaryl or like group. Such groups will generally be of up to 12 carbon atoms, more suitably up to 8 carbon atoms. Alkyl in alkyl aryl or alkylheteroary aptly contain 1 to 3 carbon atoms.

Suitable alkyl and alkenyl groups include straight or branched alkyl groups and which may include cyclic portions.

Such R groups, especially alkyl groups R, may be unsubstituted or substituted, for example, by chlorine, bromine of fluorine atoms or by lower alkoxy, lower alkylthio, lower alkylamine, dilower alkylamine groups, aryolxy, aminoaryl, lower alkyl-amino aryl groups, and for aryl or heteroaryl, by lower alkyl groups.

When used herein the term "lower" means containing 1, 2, 3, 4, 5 or 6 carbon atoms.

Particularly apt groups R include methyl, ethyl, 2-methoxyethyl, 2-ethoxylethyl, benzyl and substituted benzyl where the substituents are 1, 2 or 3 groups selected from chlorine, bromine, fluorine, methoxy, ethoxy, methyl or ethyl.

Certain apt groups R will be chiral.

A preferred group R is the methyl group.

Compounds of the formulae (IV), (V), (VI) and particularly (VIII) form important aspects of this invention. The invention also provides the use of the compounds of the formulae (IV), (V), (VI) and particularly (VIII) as useful intermediates in the preparation of voriconazole. In such compounds R may have the values given above particularly methyl.

The pyrimidine of the formula (VI) is a key compound in the present invention. The substituent X is aptly a good leaving group such as a chlorine, bromine, iodine, triflate or tosylate or the like. Preferably X is bromine. The compound of Formula (VI), as a racemate, may be prepared from compound (II) as depicted in Scheme I. The 4(6)-chloro compound (III) is obtained from compound (II) in reaction with phosphorus oxychloride. Treatment of the 4(6)-chloro compound (III) with sodium hydrosulfide provides the corresponding thiol (IV). The substitution of H in SH by SR (V) is effected by reaction with X^1-R where X^1 is a good leaving group such as one mentioned above. A particularly favoured compound X^1-R is iodomethane. Halogenation under radical conditions provides the key intermediate (VI) where X is Br, Cl or I. Other compounds of formula (VI) where X is an alternative leaving group can be made by conventional chemistry. Compounds where X is Br or Cl can serve as substrate for halogen exchange reactions or for conversion to derivatives with alternative, displaceable groups.

When the compound of Formula (III) is treated with a thiolate such as R-S-Na, chemoselective reaction in the pyrimidine 4(6)-position occurs with formation of a 4(6)-sulfide (V).

The nature of the R-substituent affects physicochemical properties, and hence yields in reactions, and very importantly, it affects the stereoselectivities of the following reactions. The stereoselectivities can further be affected by using sulfides where the R-substituent has at least one stereogenic center and is enantiomerically homogenous.

As already stated, in a preferred case, the R-substituent is a methyl group. The methyl sulfide is readily prepared as described above. Benzyl or substituted benzyl sulfides are also very readily available and apt for uses. Sulfide enantiomers can either be prepared by S-alkylation of a pyrimidine-4(6)-thione, or more generally by the reaction of a thiol enantiomer with a 4(6)-halogenopyrimidine.

A particularly favoured aspect of this invention comprises the reaction of a compound of the formula (VIII) with a reducing agent to produce a compound of the formula (IX).

This reaction may be effected with conventional reducing agents such as Raney nickel. The reaction may be effected in a solvent such as an alkanol, for example methanol, ethanol or a propanol of which ethanol is preferred. The reaction is effected at a non-extreme temperature, for example , 5°C - 70°C , 5°C - 30°C, 10°C -70°C more aptly 10°C - 25°C. Most aptly the reaction is carried out at ambient temperature.

A further particularly favoured aspect of this invention comprises the reaction of a compound of the formula (VI) with the compound of the formula (VII) to produce a compound of the formula (VIII).

This reaction is generally effected in the present of a metal reagent, for example zinc or magnesium of which zinc is preferred. The zinc will most suitably be finely divided, for example as zinc dust. Lead may be present as an additional reagent. This reaction is preferably performed in an inert solvent such as dry tetrahydrofuran.

The reaction is aptly carried out under an inert atmosphere, for example under nitrogen or argon. Iodine is aptly employed to enhance the reaction.

The reaction is most suitably performed at, for example -10°C to 70°C, - 5°C to 15°C, most suitably 0°C - 10°C, for example 0°C to 2°C.

The reaction yields are sufficiently high to obtain the desired product without needing to resort to chromatographic purification.

Examples

HPLC and LC-MS analyses were performed on a Dionex HPLC Module with a Dionex UVD 170U Detector and ThermoFinnigan MS. Column: Phenomenex Gemini C18, 4.6 x 50 mm, Mobile phase A: 0.1% aqueous formic acid, Mobile phase B: acetonitrile. Flow: 1 ml/min, Injection volume: 5-20 µl, UV-detection: 254 nm, Gradient: 0 to 100% B in 5 min, ZQ with APCI-, APCI+, MS 100-850, Cone V30. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d6 as solvent and internal standard on a Varian Gemini 300 spectrometer operating at 300 MHz or a Varian INOVA spectrometer operating at 600 MHz.

Example 1

4-Chloro-6-ethyl-5-fluoropyrimidine, compound of Formula (III)

Phosphorus oxychloride (47.2 g, 0.31 mol) was added slowly over 3 h to a mixture of 6-ethyl-5-fluoropyrimidin-4(1H)-one (40.0 g, 0.28 mol), triethylamine (28.4 g, 0.28 mol) and dichloromethane (120 ml), maintaining the reaction temperature below 40 °C. The mixture was heated at reflux for 5 h and cooled to 25 °C. The mixture was slowly poured into aqueous hydrochloric acid (3 N, 176 ml), while the temperature was kept below 20 °C. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water (50 ml), and the organic layer was concentrated at reduced pressure. Yield: 40.7 g (90%) of an oil. Purity, HPLC: 99.8% (RT=4.98 min).

Example 2

6-Ethyl-5-fluoropyrimidine-4-thiol, compound of Formula (IV)

Sodium hydrosulfide hydrate (5 M aq. sol., 43 ml, 0.21 mol) was dissolved in methanol (25 ml), and the mixture was heated to 50 °C. A solution of 4-chloro-6-ethyl-5-fluoropyrimidine (26.4 g, 0.16 mol) in methanol (40 ml) was added over 30 min. The reaction mixture was heated at 50 °C for 2 h, and additional sodium hydrosulfide hydrate (2.56 g, 34 mmol) was added in one portion. The mixture was stirred for 1 h 45 min at 50 °C and cooled to rt.

Approximately 60 ml of solvent was removed at reduced pressure. Water (200 ml) and aqueous hydrochloric acid (1 M, 75 ml) were added, and the mixture was stirred for 10 min. The precipitate was isolated by filtration and washed with water. Drying at reduced pressure overnight at 45 °C afforded 23.8 g (91% yield) of the title compound as a pale yellow crystalline solid. Purity, HPLC: >99.9% (RT=3.92 min). MS, *m/z* (% rel. int.): 143.1 (8), 159.1 (100, $[M+H]^+$), 175.0 (5), 315.0 (7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (1H, s), 2.74 (2H, q, J 7.3 Hz), 1.28 (3H, t, 7.3 Hz).

Example 3

4-Ethyl-5-fluoro-6-(methylthio)pyrimidine, compound of Formula (V), R = methyl.

6-Ethyl-5-fluoropyrimidine-4-thiol (73.9 g, 0.47 mol) was dissolved in DMF (450 ml) and cooled in an ice-bath. Iodomethane (73.0 g, 32.0 ml, 0.51 mol) was added over 3 min. The mixture was allowed to reach rt and stirred over the weekend. Cold water was added, and the product was extracted into diisopropyl ether (500 ml, 200 ml, 2 x 150 ml). The combined organic layers were washed with aqueous sodium thiosulfate (1 M, 150 ml) and brine (200 ml), and dried with sodium sulfate (180 g). The mixture was filtered and the filtrate concentrated at reduced pressure. Purification by distillation (13.2-13.5 mbar, Bp 91-92 °C) provided 76.1 g (95% yield) of the title compound as a colourless liquid. Purity, HPLC: >99.9% (RT=5.29 min). MS, *m/z* (% rel. int.): 172.9 (100, $[M+H]^+$), 214.0 (15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (1H, s), 2.77 (2H, q, J 7.3 Hz), 2.56 (3H, s), 1.27 (3H, t, J 7.3 Hz).

Example 4

4-(1-Bromoethyl)-5-fluoro-6-(methylthio)pyrimidine, compound of Formula (VI), R = methyl, X = bromine.

A mixture of 4-ethyl-5-fluoro-6-(methylthio)pyrimidine (40.8 g, 0.24 mol), N-bromosuccinimide (NBS) (52.7 g, 0.30 mol), α,α'-azoisobutyronitrile (AIBN) (0.49 g, 3.0 mmol) and methyl acetate (300 ml) was heated at reflux under argon atmosphere. After 3 h additional AIBN (0.49 g, 3.0 mmol) in methyl acetate (10 ml) was added. The mixture was stirred overnight and cooled to rt. The mixture was poured into aqueous sodium metabisulfite (0.5 M, 300 ml), the layers separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 ml). The combined organic phases were washed with brine (200 ml), and dried (Na_2SO_4). The solvent was partially evaporated at reduced pressure, petroleum ether (250 ml) was added, and the mixture was stirred for 10 min. The precipitate (succinimide) was filtered off and rinsed with petroleum ether/ethyl acetate (9:1, 3 x 20 ml). Concentration of the filtrate *in vacuo* afforded a crude material (83.5% pure by HPLC, RT=5.67 min) which was purified by distillation. The product was collected in 4 fractions: Fraction 1: 0.39 g (0.7% yield), 96.5% pure by HPLC (bp. 92-102 °C, 0.84-0.55 mbar), Fraction 2: 7.15 g (12%), 96.9% pure (bp. 92-102 °C, 0.84-0.55 mbar), Fraction 3: 38,9 g (65%), 97.1% pure (bp. 105-106 °C, 0.25-0.16 mbar), Fraction 4: 9.23 g (16%), 88.2% pure (bp. 100-98 °C, 0.16 mbar). Total yield: 55.7 g (94% yield). MS, *m/z* (% rel. int.): 171.2 (4), 251.0 (100, $[M+H]^+$), 292.0 (12). ^1H NMR (300 MHz, $CDCl_3$): δ 8.74 (1H, s), 5.32 (1H, q, J 6.6 Hz), 2.59 (3H, s), 2.03 (3H, d, J 6.6 Hz).

Example 5

(2R,3S/2S,3R)-2-(2,4-Difluorophenyl)-3-[5-fluoro-6-(methylthio)pyrimidin-4-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, compound of Formula VIII, R = methyl.

A mixture of zinc dust (3.27 g, 50.0 mmol), lead (0.16 g, 0.79 mmol) and dry THF (18 ml) was stirred at rt in inert atmosphere for 10 min. A solution of iodine (2.28 g, 9.0 mmol) in dry THF (9 ml) was added over 7 min. The reaction mixture was cooled to 2 °C, and a solution of 4-(1-bromoethyl)-5-fluoro-6-(methylthio)pyrimidine (2.93 g, 11.7 mmol), 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (2.23 g, 10.0 mmol) and iodine (0.25 g, 1.0 mmol) in dry THF (18 ml) was added over 10 min. The temperature in the mixture was maintained below +10 °C during the addition. The mixture was stirred for 1 h 30 min below +5 °C. LC/MS analysis demonstrated full consumption of starting material and formation of the desired compound as a mixture of diastereoisomers. Acetic acid (2.9 ml) and water (30 ml) were added while maintaining the temperature below 25 °C. The mixture was poured into ethyl acetate (100 ml) and stirred for 15 min. The solvents were removed at reduced pressure, and ethyl acetate was added. Aqueous sodium hydrogencarbonate (~100 ml) was added until pH 8, the solids filtered off, and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 ml), and the combined organic layers were washed with aqueous sodium thiosulfate (1 M, 50 ml), brine (150 ml), and dried (Na_2SO_4). Removal of the solvents *in vacuo* left 4.26 g of crude material as a white solid, diastereoisomer ratio: 9.5 : 1 in favor of the (2R,3S/2S,3R) enantiomeric pair (RT(2R,3R/2S,3S)=5.36 min, RT(2R,3S/2S,3R)=5.68 min). The crude material (4.26 g) was dissolved in ethyl acetate (6 ml) at reflux temperature. Heptane (90 ml) was added at this temperature, and the mixture was stirred at 90 °C for 3 min when a clear solution was obtained. The mixture was allowed to cool to rt overnight while stirring. The crystalline product thus formed was collected by filtration and rinsed twice with heptane (2 x 10 ml). Drying at 50 °C at reduced pressure afforded 3.14 g (79% yield) of a white solid. Purity: 97.5% by HPLC. The unwanted enantiomeric pair amounted to 0.18%. MS, *m/z* (% rel. int.): 173.1 (10), 224.1 (36), 265.0 (10), 396.2 (100, $[M+H]^+$), 437.2 (38). ^1H NMR (300 MHz, DMSO-d6): δ 8.84 (1H, s), 8.23 (1H, s), 7.61 (1H, s), 7.28 (1H, q, J 8.8 Hz), 7.19 (1H, t, J 9.5 Hz), 6.92 (1H, t, J 8.8 Hz), 6.04 (1H, bs), 4.76 (1H, d, J 14.6 Hz), 4.35 (1H, d, J 14.6 Hz), 3.85 (1H, q, J 6.6 Hz), 2.61 (3H, s), 1.08 (3H, d, J 6.6 Hz).

Example 6

(2R,3S/2S,3R)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, compound of Formula (IX).

(2R,3S/2S,3R)-2-(2,4-Difluorophenyl)-3-[5-fluoro-6-(methylthio)pyrimidin-4-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (3.95 g, 10.0 mmol) was dissolved in methanol (30 ml), and the solution was heated to 30 °C (internal temperature control). A suspension of Raney nickel (27.7 g, previously washed with 3 x 20 ml methanol) in methanol (20 ml) was added, and the mixture was stirred for 1 h 40 min. At this point HPLC indicated 93.5% product and 4.0% starting material in the reaction mixture. The mixture was cooled to 20 °C, and nickel was removed by filtration through celite. The filter cake was washed with methanol, and the combined filtrate was concentrated at reduced pressure.

Drying of the residue *in vacuo* at 50 °C for 3 h afforded 2.39 g (68% yield) of the title compound. Purity, HPLC: 91.5% (RT=4.91 min). MS, *m/z* (% rel. int.): 224.1 (8), 265.2 (24), 350.3 (70, [M+H]$^+$), 391.2 (100), 507.8 (10), 624.4 (15).

Example 7

(2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (voriconazole)

To a solution of the racemic material obtained above (1.28 g, 3.66 mmol) in acetone (29 ml) was added a solution of (1R)-10-camphorsulfonic acid (0.85 g, 3.66 mmol) in methanol (9.6 ml). The solvents were removed at reduced pressure, and the residue was dissolved in a mixture of acetone (10 ml) and methanol (2 ml). Crystals formed spontaneously after 3 h. Acetone (10 ml) was added, and the mixture was stirred overnight. The solid was isolated by filtration, washed with a small amount of acetone and dried. The solid was dissolved in a mixture of acetone (14 ml) and methanol (4 ml) at reflux. The solution was cooled to rt and stirred for 90 min. Isolation of the precipitate formed by filtration, washing with acetone and drying afforded 0.72 g of the acid addition salt. 0.70 g of the solid material was taken up in dichloromethane (10 ml) and water (10 ml), and the pH was adjusted to 11 by addition of aqueous sodium hydroxide (15% sol.). The layers were separated, and the aqueous layer was extracted with dichloromethane (5 ml). The combined organic layers were washed with water (3 x 10 ml) and brine, and dried (sodium sulfate). Concentration at reduced pressure afforded 0.36 g (28% yield, 56% of the available enantiomer) of voriconazole as a white crystalline solid. Purity, HPLC: 99.8% (RT=4.91 min). Mp. 122.6 °C (Lit. 134 °C). MS, *m/z* (% rel. int.): 224.0 (27), 350.1 (100), 391.0 (10). ^{1}H NMR (600 MHz, DMSO-d6): δ 9.02 (1H, d, J 3.0 Hz), 8.83 (1H, d, J 1.8 Hz), 8.21 (1H, s), 7.59 (1H, s), 7.24 (1H, ddd, J 7.0 Hz, J 9.0 Hz, J 9.0 Hz), 7.16 (1H, ddd, J 2.4 Hz, J 9.0 Hz, J 11.8 Hz), 6.89 (1H, ddd, J 2.4 Hz, J 8.4 Hz, J 8.4 Hz), 5.95 (1H, s), 4.77 (1H, d, J 14.4 Hz), 4.31 (1H, d, J 14.4 Hz), 3.90 (1H, q, J 7.0 Hz), 1.08 (3H, d, J 7.0 Hz).

Example 8

4-(1-Bromoethyl)-5-fluoro-6-(methylthio)pyrimidine, crude material, compound of Formula (VI), R = methyl, X = bromine.

A mixture of 4-ethyl-5-fluoro-6-(methylthio)pyrimidine (20.2 g, 0.12 mol), NBS (26.1 g, 0.15 mol), AIBN (576 mg, 3.5 mmol, 2.3 mol%) and methyl acetate (100 ml) was heated at reflux for 22 h under argon atmosphere. The mixture was poured into aqueous sodium metabisulfite (0.5 M, 150 ml), and the layers were separated. The aqueous layer was extracted with methyl acetate (2 x 50 ml). The combined organic layers were washed with brine, and concentrated at reduced pressure to about 150 ml. Heptane (120 ml) was added, and the mixture was stirred for 10 min. The precipitate (succinimide) was filtered off and rinsed with heptane (2 x 10 ml), and the filtrate was concentrated at reduced pressure. The material was redissolved in toluene (50 ml) and concentrated at reduced pressure three times, providing 30.0 g (>100%, theoretical yield: 29.5 g) of a crude material that was used in Example 9 without further purification. Purity: 88.9% by HPLC (RT=5.65 min).

Example 9

(2R,3S/2S,3R)-2-(2,4-Difluorophenyl)-3-[5-fluoro-6-(methylthio)pyrimidin-4-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, compound of Formula VIII, R = methyl.

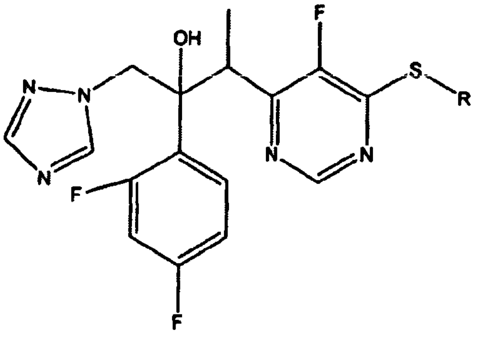
A mixture of zinc dust (31.9 g, 0.49 mol), lead (1.59 g, 7.7 mmol, 5 wt% to zinc) and THF (175 ml) was stirred vigorously at rt under inert atmosphere for 1 h. A solution of iodine (22.3 g, 87.9 mmol) in THF (85 ml) was added over 22 min, and the mixture was cooled to 0 °C. A solution of 4-(1-bromoethyl)-5-fluoro-6-(methylthio)pyrimidine (30.0 g, crude material as obtained in Example 8, 0.12 mol theoretical amount), iodine (2.48 g, 9.77 mmol) and 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (21.8 g, 97.7 mmol, HPLC RT=4.21 min) in THF (175 ml) was added over 14 min. The temperature was kept below 6 °C during the addition. The reaction mixture was stirred at ~1 °C for 45 min. HPLC indicated full conversion of the starting material and formation of the target compound as a mixture of diastereomers in a ratio of 10 : 1 in favour of the desired (2R,3S/2S,3R)-

enantiomeric pair. The mixture was allowed to warm to 10-15 °C, and a solution of acetic acid (5.9 ml) in water (20 ml) was added while maintaining the temperature below 25 °C. Saturated aqueous sodium carbonate (150 ml) was added whereupon a precipitate was formed. The solids were filtered off and rinsed with ethyl acetate (3 x 50 ml). THF was removed from the filtrate by concentration at reduced pressure until water started to distill. Ethyl acetate (300 ml) and water (100 ml) were added, the layers separated, and the aqueous layer extracted with ethyl acetate (50 ml). The combined organic layers were washed with an aqueous solution of EDTA disodium salt dihydrate (2 wt%, 300 ml), aqueous sodium thiosulfate (1 M, 150 ml), and brine (200 ml). The organic layer was concentrated at reduced pressure. Dissolution of the residue in toluene (100 ml) and reconcentration was carried out twice, and 42.9 g (>100% yield, theoretical yield: 38.6 g) of an off-white solid was obtained. Diastereomeric ratio (HPLC): 10 : 1.

The crude material (42.9 g) was dissolved in ethyl acetate (50 ml) at reflux, and heptane (500 ml) was added slowly at this temperature. The mixture was stirred at 95 °C for 5 min and allowed to cool to rt overnight with stirring. A crystalline solid was collected by filtration and rinsed with heptane (3 x 20 ml). Drying at 50 °C and reduced pressure for 1 h afforded 35.1 g (91% yield from 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone) of the title compound as an off-white solid. Purity: 91.1% by HPLC (RT=5.64 min). The unwanted (2R,3R/2S,3S)-enantiomeric pair was not detected by HPLC after the crystallisation. Subjecting the isolated material to a second crystallisation provided material with a purity of 94.3% in 79.5% yield.

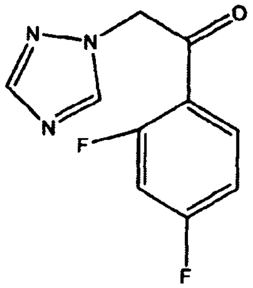
Claims

1. A process for the preparation of a compound of the formula (VIII):



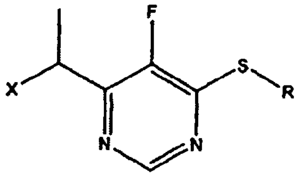
(VIII)

which comprises the coupling of a compound of formula (VII):



(VII)

with a compound of the formula (VI):



(VI)

wherein R is a C_{1-12} alkyl (aptly C_{1-6} alkyl), C_{2-12} alkenyl, C_{1-3} alkylaryl, aryl, heterocyclic, C_{1-3} alkylheterocyclic, C_{1-12} alkyl substituted by C_{1-6} alkoxy, C_{1-12} alkylthio, C_{1-12} alkylamino, C_{1-12} dialkylamino, COC_{1-12} alkyl, aryl, aryloxy or an O-C_{1-6} alkylaryl group wherein any aryl group may be substituted with 1, 2 or 3 groups selected from chlorine, bromine, fluorine, methoxy, ethoxy, methyl or ethyl.

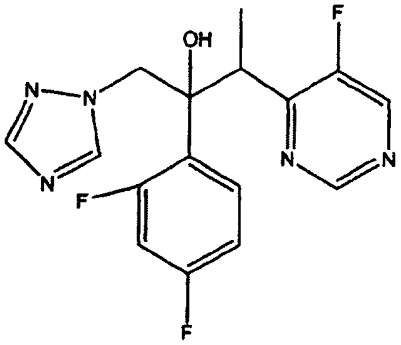
2. A process as claimed in Claim 1 wherein R is methyl.

3. A process as claimed in Claim 1 wherein the coupling is effected using activated zinc and iodine.

4. A process as claimed in any of Claims 1 to 3 carried out at -10°C to 70°C or preferably at -10°C to 25 °C.

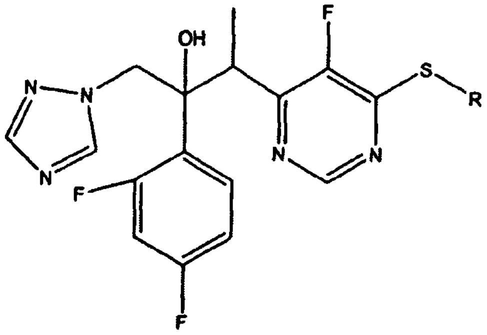
5. A process as claimed in any of Claims 1 to 4 wherein the solvent is methyl acetate, ethyl acetate, or other aprotic solvent such as tetrahydrofuran.

6. A process for the preparation of a compound of the formula (IX):



(IX)

wherein a compound of the formula (VIII):



(VIII)

is reduced;
wherein R is as defined in Claim 1.

7. A process as claimed in Claim 6 wherein R is methyl.

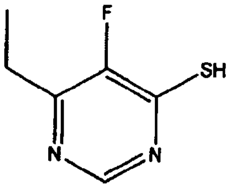
8. A process as claimed in Claim 6 or 7 wherein reduction is effected with Raney nickel.

9. A process as claimed in any of Claims 6 to 8 wherein the reduction is effected at 10°C to 70°C or preferably at 10°C to 30°C.

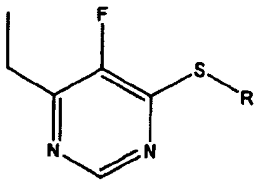
10. A process as claimed in any of Claims 6 to 9 wherein the solvent is ethanol.

11. A process as claimed in any of Claims 6-10 wherein the compound of formula (VIII) is prepared by a process as claimed in any of Claims 1 to 5.

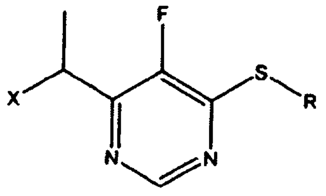
12. A compound of the formula (IV), (V) or (VI):



(IV)



(V)



(VI)

wherein X is Cl, Br, I, OCOR^2 or OSO$_2$R^2 wherein R^2 is C$_{1-6}$ alkyl or aryl such as phenyl or tolyl or trifluoromethanesulfonate.

13. A compound of the formula (V) or (VI) as defined in Claim 12 wherein R is methyl.

14. A compound of the formula (VI) as defined in Claim 12 or 13 wherein X is Br.

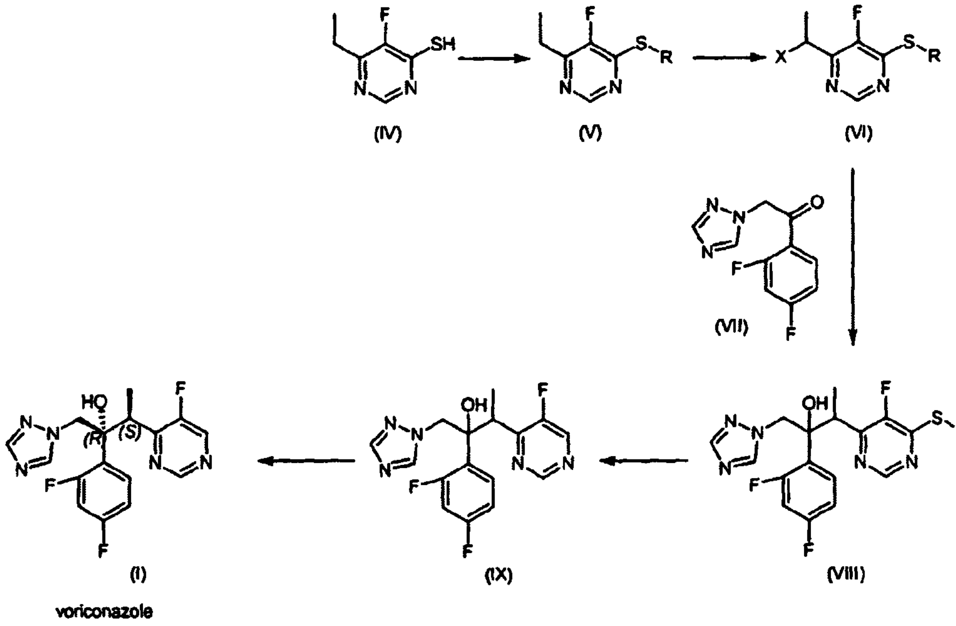
15. A compound of the formula (IV), (V), or (VI) as defined in Claim 12 for use as an intermediate in the synthesis of a compound of the formula (VIII) as defined in Claim 1.

16. A compound of the formula VIII as defined in claim 1.

17. The use of the compound of the formula VIII as defined in claim 1 as a chemical intermediate in the manufacture of voriconazole.

18. A process as claimed in claim 6 wherein a compound of the formula (IX) is resolved to provide voriconazole.

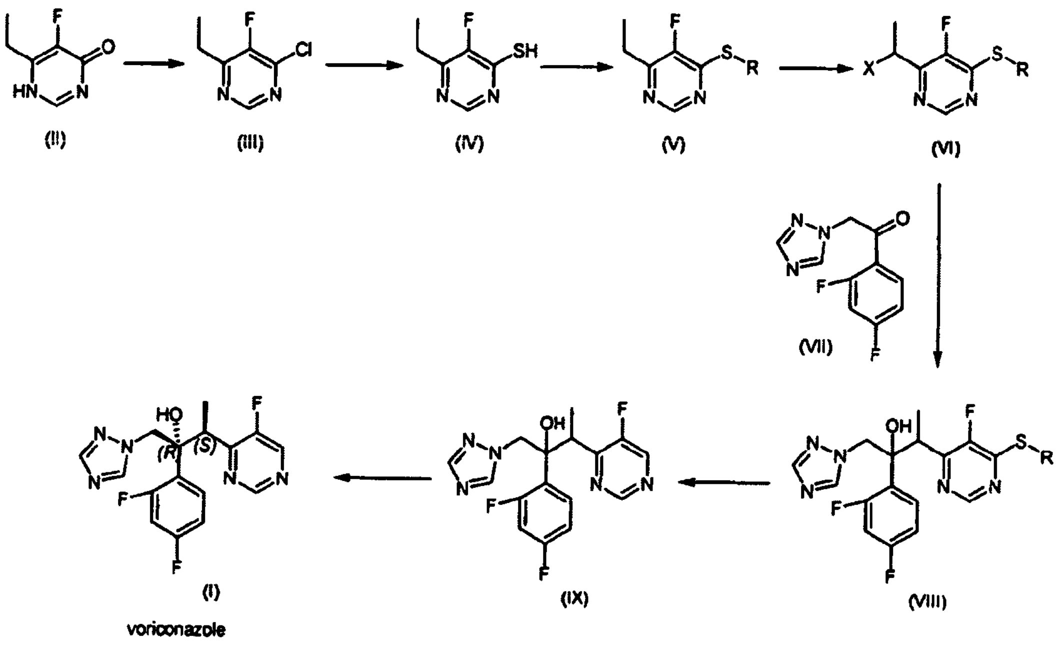
19. A process for the preparation of voriconazole which comprises:



Scheme I.

wherein R and X are as defined in claim 1.

20. A process for the preparation of voriconazole which comprises:



Scheme I.

wherein R and X are as defined in claim 1.

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Application No: GB0716298.5 **Examiner:** Dr Simon Grand
Claims searched: 1-20 **Date of search:** 25 February 2008

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	CN1473825 A (ZHANG) See whole document and CAS Abstract Acc. No.2004:1010085.
A	-	CN1919846 A (ZHOU et al.) See whole document and CAS Abstract Acc. No.2007:240794.
A	-	Zhongguo Yiyao Gongye Zazhi, 2005, Vol.36(10), Wang et al., pp.653-655. See whole document especially p.654.
A	-	Organic Process Research & Development, 2001, Vol.5(1), Butters et al., pp.28-36. See whole document.
A	-	WO 93/07139 A1 (PFIZER) See whole document.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
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&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

C07D

The following online and other databases have been used in the preparation of this search report

ONLINE: EPODOC, WPI, CAS-ONLINE, MARPAT.

International Classification:

Subclass	Subgroup	Valid From
C07D	0403/06	01/01/2006

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Subclass	Subgroup	Valid From
C07D	0239/38	01/01/2006