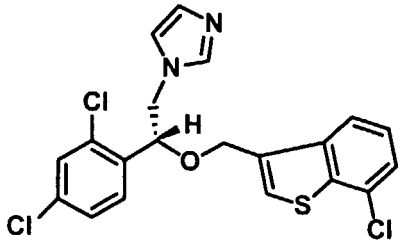
R-(-)-1-[2-(7-CHLOROBENZO[b]THIOPHEN-3-YL-METHOXY)-2-(2,4-DICHLOROPHENYL)-ETHYL]-1*H*-IMIDAZOLE

DESCRIPTION

The present invention relates to R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-*1H*-imidazole (R-(-)-sertaconazole) and its salts, a process for its preparation, compositions which comprise said compound and the use of same for treating fungal infections and combating crop diseases.

Racemic 1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1*H*-imidazole - a compound known as sertaconazole (WHO, INN) - is a useful antifungal agent for treatment of diseases caused by fungi and yeasts in man and in animals. Its preparation and that of its mononitrate are disclosed in European Patent No. 151.477.

The present invention relates to R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-*1H*-imidazole of formula (I):



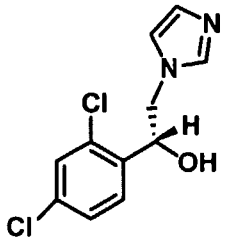
(I)

as well as its pharmaceutically acceptable addition salts.

The R-(-)-enantiomer of sertaconazole possesses an activity of about 2 times higher than that of the racemic mixture, against both fungi and yeasts (because its affinity to the target is 2 times higher) as shown in Table 1. This finding has enabled to formulate R-(-)-sertaconazole at doses ½ of those used for racemic sertaconazole, thus providing a reduced risk of side effects and the suppression of unspecific toxicity due to the unwanted fraction of the S-(+)-enantiomer.

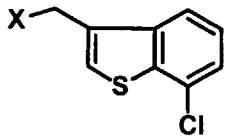
The mononitrate is the preferred salt of R-(-)-sertaconazole.

The present invention also relates to a process for the preparation of the R-(-)-enantiomer of sertaconazole and its pharmaceutically acceptable addition salts which process comprises reacting R-(-)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol of formula ((R)-(-)-III):



((R)-(-)-III)

with 3-halomethyl-7-chlorobenzo[b]thiophene of formula (IV):



(IV)

wherein X is halogen.

The compound can be recovered from the reaction mixture in a manner known per se. If desired, the crude product can be further purified by methods well known in the art, e.g. crystallisation and/or chromatography.

The preparation of the S-(+)-enantiomer of sertaconazole can be accomplished accordingly using S-(+)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol instead of the R-(-)-enantiomer.

A prerequisite for the preparation of the enantiomers of sertaconazole according to the above process is to prepare the appropriate enantiomers of intermediate 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol (III).

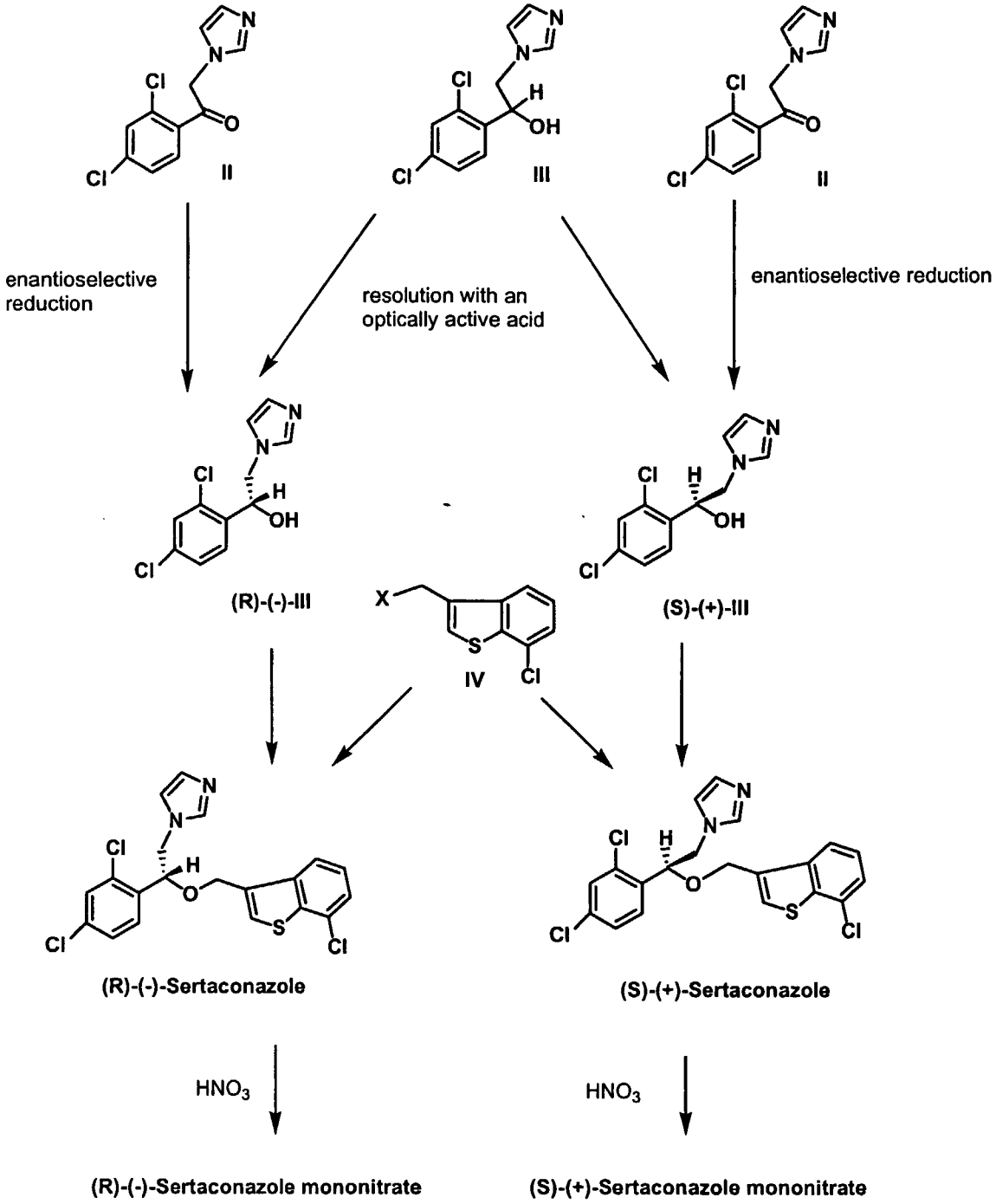
The two enantiomers of 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol (III) can be prepared by resolution of the corresponding racemic mixture with an optically active

acid, preferably L-tartaric acid, D-tartaric acid, dibenzoyl-L-tartaric, dibenzoyl-D-tartaric acid or the like, according to the method described in GB Patent No. 1.244.530 and in Lämmerhofer M. and Lindner W. (Chirality 6:261-269, 1994). (R)-(-)-1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanol is also prepared by the enantioselective reduction of 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanone (II) using (-)-β-chlorodiisopino-camphenylborane, [(-)-DIP chloride] leading to (R)-(-)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol ((R-(-)-III) with an acceptable optical purity.

The reaction of one of the enantiomers of the intermediate of formula (III) with 3-halomethyl-7-chlorobenzo[b] thiophene (IV) is carried out to yield the corresponding enantiomer of sertaconazole as free base. Among 3-halomethyl-7-chlorobenzo[b]thiophenes, 3-chloromethyl-7-chlorobenzo[b]thiophene and 3-bromomethyl-7-chloro-benzo[b]tiophene are preferred.

The enantiomers of sertaconazole as free bases can be converted into the pharmaceutically acceptable salts in a manner known per se. Preferably, the mononitrates are obtained by treating with nitric acid.

The reaction steps for the preparation of the enantiomers of sertaconazole are shown in the following scheme.



The present invention further relates to pharmaceutical compositions comprising R-(-)-sertaconazole and/or a salt thereof and to the use of R-(-)-sertaconazole and/or a salt thereof for the treatment of infections caused by fungi and yeasts in both the man and pets, as well as against crop diseases caused by such microorganisms.

The compounds of the present invention, optionally mixed with pharmacologically acceptable carriers, can be administered to humans or animals by the oral route in the form of tablets, capsules, coated tablets, syrups, solutions, powders, granules, emulsions, oral gels, oral pastes, buccopharyngeal solutions, buccopharyngeal suspensions, buccopharyngeal gels, buccopharyngeal pastes, etc., by injectable route, by rectal route and by vaginal-intrauterine route in the form of ovulum, vaginal tablet, vaginal capsule, medicated vaginal tampon, ointment, cream, gel, foam, solution, emulsion, suspension, pessary, lotion, etc., at daily doses ranging from 50 to 400 mg; and by topical route in the form of cream, lotion, paste, suspension, ointment, emulsion, solution, foam, shampoo, powder, gel, etc., at concentrations ranging from 0.05 to 3%.

Also the compounds of the present invention, optionally in admixture with a diluent or carrier when used against crop

diseases can be applied by watering, atomising, spraying, dusting, or in the form of powder, cream, paste, etc., at the rate of 0.05 - 10 Kg per hectare of soil.

The following Examples will illustrate the preparation of the enantiomers of sertaconazole, pharmaceutical formulations containing them and their biological activity on various microorganisms.

Example 1: R-(-)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol

In a 50-ml one-necked flask equipped with an addition funnel, cooling bath, magnetic stirrer and nitrogen gassing device 3.14 g (9.8 mmol, 2.5 eq.) of (-)-DIP chloride and 9 ml of anhydrous ethyl ether (molecular screens 4Å) are mixed. To the resultant mixture, a solution of 1 g (3.92 mmol, 1 eq.) of 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanone in 10 ml of anhydrous tetrahydrofuran (molecular screens 4Å) is added drop by drop at room temperature under nitrogen atmosphere. The mixture is stirred for 24 hours at room temperature under nitrogen atmosphere. 0.4 ml of methanol are added, stirred for 10 min, and the solvents are removed by reduced-pressure evaporation.

To the resultant crude, 10 ml of n-hexane and 10 ml of water are added. The mixture is acidified by adding 1.6 ml of 6 M hydrochloric acid. The two phases are separated and

the organic layer is removed. The aqueous phase is neutralised with 3M NaOH until pH = 10-11 in the presence of 10 ml of ethyl ether. The two phases are separated, and the organic layer is washed with 10 ml of ethyl ether. The two ethereal layers are dried over anhydrous sodium sulphate and evaporated to dryness by reduced-pressure distillation. 1.27 g of crude product are yielded and crystallised from a mixture of 5 ml of ethanol-water 1:1 v/v to give 0.8 g (R= 80%) of (R)-(-)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol.

Analytical data:

DSC: peak at 107.4°C

IR spectrum: conforms

^{1}H-^{13}C-NMR (DMSO) spectrum: conforms

$[\alpha]_D^{20}$ (c = 1%, MeOH) = -80

Example 2: (R)-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole

In a 100-ml three-necked flask equipped with a reflux cooler, immersion thermometer, addition funnel, cooling bath, and nitrogen gassing device 10 ml of dry N,N-dimethylformamide (molecular screens 4Å) and 1.27 g (11.3 mmol, 1.03 eq.) of potassium t-butoxide are mixed. To the resultant mixture, cooled in a water bath, a solution of 2.83 g (11 mmol) of (R)-(-)-1-(2,4-dichlorophenyl)-2-

imidazol-1-yl-ethanol in 15 ml of dry N,N-dimethylformamide are added drop by drop. After the addition is completed, the mixture is stirred for 45 minutes and added to a solution of 2.93 g (11.2 mmol, 1.02 eq.) of 3-bromomethyl-7-chlorobenzo[b]thiophene in 7 ml of dry N,N-dimethylformamide. The reaction mixture is stirred for 4 hours at room temperature. The solvent is evaporated by reduced-pressure distillation and the residue is treated with 50 ml of methylene chloride. The resultant solution is washed twice with 30 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness by reduced-pressure distillation to yield 4.62 g of crude product.

The crude product obtained is purified by silicagel column chromatography using a gradient of methylene chloride-methanol as an eluant. A resin (2.0 g) is obtained which is crystallised from ethyl ether (10 ml). The solid formed is filtered and dried to give 1.22 g (R = 25.1 %) of (R)-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole.

Analytical data:

DSC: peak at 74.5°C

IR spectrum: conforms

^{1}H-^{13}C-NMR (DMSO) spectrum: conforms

$[\alpha]_D^{20}$ (c = 1%, MeOH) = -61.0

Example 3: (S)-(+)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole

In a 100-ml three-necked flask equipped with a reflux cooler, immersion thermometer, addition funnel, cooling bath, and nitrogen gassing device 16 ml of dry N,N-dimethylformamide (molecular screens 4Å) and 2.04 g (18.43 mmol, 1.05 eq.) of potassium t-butoxide are mixed. To the resultant mixture, cooled in a water bath, a solution of 4.44 g (17.2 mmol) of (S)-(+)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol in 25 ml of dry N,N-dimethylformamide are added drop by drop. After the addition is completed, the mixture is stirred for 45 minutes and added to a solution of 4.61 g (17.62 mmol, 1.02 eq.) of 3-bromomethyl-7-chlorobenzo[b]thiophene in 13 ml of dry N,N-dimethyl-formamide. The reaction mixture is stirred for 4 hours at room temperature. The solvent is evaporated by reduced-pressure distillation and the residue is treated with 80 ml of methylene chloride. The resultant solution is washed twice with 50 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness by reduced-pressure distillation to yield 7.30 g of crude product.

The crude product obtained is purified by silicagel column chromatography using a gradient of methylene chloride-methanol as an eluant. A resin (3.78 g) is obtained which is crystallised from ethyl ether (18 ml). The solid formed

is filtered and dried to give 2.61 g (R = 34.5%) of (S)-(+)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole.

Analytical data:

DSC: peak at 83.4°C

IR spectrum: conforms

^{1}H-^{13}C-NMR (DMSO) spectrum: conforms

$[\alpha]_D^{20}$ (c = 1%, MeOH) = +69

Example 4: (R)-(-)-Sertaconazole mononitrate ((R)-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate)

880 mg (2.01 mmol) of (R)-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole are dissolved in 5 ml of 96% ethanol. 1 ml of water is added and heated at a temperature between 35 and 37°C. To the obtained solution, 0.23 ml of 60% nitric acid (3 mmol, 1.5 eq.) are added. Then 3 ml of water are added and cooled first at room temperature and thereafter at 10°C for 1 hour. The formed solid is filtered, washed twice with 4 ml of water and dried at vacuum for 24 hours to give 0.9 g (R = 89%) of (R)-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate.

Analytical data:

DSC: peak at 116.87°C

IR spectrum: conforms

^{1}H-^{13}C-NMR (DMSO) spectrum: conforms

$[\alpha]_D^{20}$ (c = 1%, MeOH) = -85.00

Example 5: (S)-(+)-Sertaconazole mononitrate ((S)-(+)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate)

2.35 mg (5.37 mmol) of (S)-(+)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole are dissolved in 17 ml of 96% ethanol. 3 ml of water are added and heated at a temperature between 35 and 40°C. To the obtained solution, 0.61 ml of 60% nitric acid (8.06 mmol, 1.5 eq.) are added. Then 13 ml of water are added and cooled first at room temperature and thereafter at 10°C for 1 hour. The formed solid is filtered, washed twice with 10 ml of water and dried at vacuum for 24 hours to give 2.65 g (R = 98.5%) of (S)-(+)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate.

Analytical data:

DSC: peak at 168.91°C

IR spectrum: conforms

^{1}H-^{13}C-NMR (DMSO) spectrum: conforms

$\alpha]_D^{20}$ (c = 1%, MeOH) = +89.00

Example 6: 1% Cream formulation

Composition for 100 g	
R-(-)-Sertaconazole mononitrate	1.00 g
Palmitic and stearic acid mono- and diglyceride	6.00 g
Ketostearyl alcohol with 20 mol of ethylene oxide	1.00 g
Oleic acid decyl ester	5.00 g
Undecylenic acid monoethanolamine	2.00 g
Carbomer	1.00 g
Triethanolamine	0.60 g
Methylparaben	0.15 g
Propylparaben	0.05 g
Distilled water to volume	100.00 g

Example 7: 1% Gel formulation

Composition for 100 g	
R-(-)-Sertaconazole mononitrate	1.00 g
Propylene glycol	10.00 g
Carbomer	1.00 g
Tween 20	0.10 g
Phenoxyethanol	0.35 g
EDTA disodium	0.15 g
Citric acid	0.25 g
1 N Sodium hydroxide	1.50 g
Triethanolamine	1.55 g
Distilled water to volume	100.00 g

Example 8: Biological data

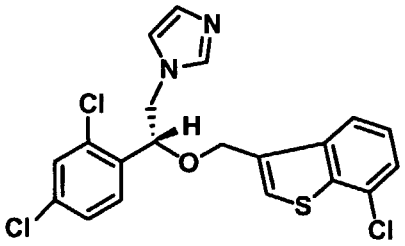
Minimal Inhibitory Concentrations (MICs) were determined by using a modification of the microdilution method M27-A recommended by the National Committee for Clinical Laboratory Standards in RPMI-1640 medium (Sigma) supplemented with glucose to a concentration of 2% and adjusted to pH 7.0 with 0.165 M morpholine propanesulfonic (MOPS) acid buffer. Serial twofold dilutions were made in modified RPMI-1640 medium from stock solutions. MICs were defined as the lowest drug concentrations resulting in 50% inhibition of growth compared to that of the growth control. The microbiological activities, expressed as geometric means, of R-(-)sertaconazole in comparison with the S-(+)-enantiomer, which is much less active, and with racemic sertaconazole are shown in Table 1. The number of strains used in the experiments is given in parenthesis below the name of each microorganism.

Table 1

MIC (µg/ml) of Sertaconazole nitrate and its enantiomers			
Microorganism	R-(-)enantiomer	Racemate	S-(+)enantiomer
Candida spp (42)	0.125	0.256	3.217
Dermatophytes (17)	0.04	0.08	0.17
Filamentous fungi (11)	1.76	3.11	16
Malassezia spp (11)	0.64	1.37	10.96

CLAIMS

1. R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole of formula (I):

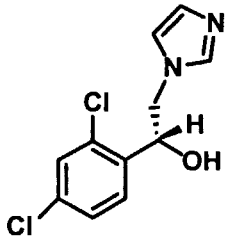


(I)

and pharmaceutically acceptable salts thereof.

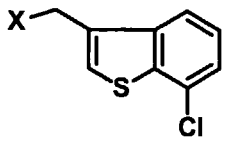
2. R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate.

3. A process for preparing a compound according to claim 1 or claim 2, comprising reacting R-(-)-1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol of formula ((R)-(-)-III):



((R)-(-)-III)

with 3-halomethyl-7-chlorobenzo[b]thiophene of formula (IV):



(IV)

wherein X is halogen, and optionally treating the resulting R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole with a salt-forming acid.

4. A process according to claim 3, wherein X is chlorine or bromine.

5. A process according to claim 3 or claim 4, wherein the compound is R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate and the salt-forming acid is nitric acid.

6. A process according to any one of claims 3 to 5, wherein R-(-)-1-[2,4-dichlorophenyl)-2-imidazol-1-yl-ethanol of formula ((R)-(-)-(III) is prepared by enantioselective reduction of 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanone with (-)-β-chlorodiisopino-camphenylborane.

7. A pharmaceutical or agricultural composition comprising R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole or a salt thereof.

8. A pharmaceutical or agricultural composition comprising R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate.

9. The use of R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole or a salt thereof for the preparation of either a pharmaceutical composition for treating fungal infections in humans and animals or an agricultural composition for combating crop diseases.

10. The use of R-(-)-1-[2-(7-chlorobenzo[b]thiophen-3-yl-methoxy)-2-(2,4-dichlorophenyl)-ethyl]-1H-imidazole mononitrate for the preparation of either a pharmaceutical composition for treating fungal infections in humans and animals or an agricultural composition for combating crop diseases.