1 475 271

PATENT SPECIFICATION

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(19)

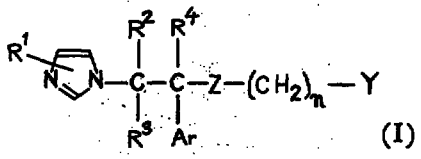


(54) NOVEL 1-ARYL-2-(1-IMIDAZOLYL)ALKYL ETHERS AND THIOETHERS AND THEIR USE AS ANTIFUNGAL AGENTS

(71) We, PFIZER LIMITED, a British Company, of Ramsgate Road, Sandwich, Kent, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to imidazole derivatives and in particular to 1 - aryl - 2 - (1-imidazolyl)alkyl ethers and thio-ethers which possess anti-fungal activity.

Thus, the present invention provides 1-aryl - 2 - (1 - imidazolyl) alkyl ethers and thio-ethers having the following general formula:—



(I)

where

R^1, R^2, R^3 and R^4 are each a hydrogen atom or a lower alkyl group;

Ar is a phenyl group, which may optionally be substituted with one or more halogen atoms, lower alkyl groups or lower alkoxy groups, or a thienyl or halothienyl group;

Z is 0 or S; n is 1 or 2;

and

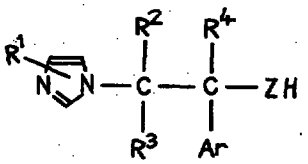
Y is an aromatic heterocyclic group, optionally substituted with one or more halogen atoms, lower alkyl groups or lower alkoxy groups

and pharmaceutically acceptable acid addition salts thereof.

The term "lower alkyl" and "lower alkoxy" refer to straight or branch chain groups having from 1 to 6 carbon atoms and halogen means fluorine, chlorine, bromine or iodine. The preferred lower alkyl and lower alkoxy groups are methyl and methoxy respectively. Ar is preferably a dihalophenyl group, particularly 2,4-dichloro-phenyl. It may also be a 2-chloro-thienyl group. Preferred aromatic heterocyclic groups are thienyl, halothienyl and thiazolyl. Preferably R^1, R^2, R^3 and R^4 are each hydrogen and n is 1.

Particularly preferred individual compounds of the present invention are 1 - [2,4 - dichloro-β - (3 - thienylmethoxy)phenethyl]imidazole, 1 - [2,4 - dichloro - β - (5 - chloro - 2-thienylmethoxy)phenethyl]imidazole, and 1-[2,4 - dichloro - β - (2 - chloro - 3 - thienylmethoxy)phenethyl]imidazole. Also preferred are 1 - [2,4 - dichloro - β - (2 - thienylmethoxy)phenethyl]imidazole, 1 - [2,4 - dichloro - β - (2,5 - dichloro - 3 - thienylmethoxy)phenethyl]imidazole, 1 - [2,4 - dichloro - β - (5 - chloro - 2 - thienylmethylthio)phenethyl]imidazole, 1 - [2,4 - dichloro-β - (3 - thienylmethylthio)phenethyl]imidazole, 1 - [2,4 - dichloro - β - (4 - thiazolylmethoxy)phenethyl]imidazole and 1 - [2 - (5-chloro - 2 - thienyl) - 2 - (3 - chloro - 2-thienylmethoxy)ethyl]imidazole.

The compounds of formula (I) may be prepared by aralkylation of an appropriate 1-aryl - 2 - (1 - imidazolyl)alkanol or alkane thiol of the formula: —



(II)

wherein R^1 to R^4, Ar and Z are as previously defined.

Such a reaction comprises converting the alcohol or thiol of formula (II) to its alkali metal derivative by treatment with a strong base, such as an alkali metal amide or hydride, and reacting with the appropriate aralkyl halide of the formula:—

$$X—(CH_2)_n—Y \qquad (III)$$

where n and Y are as previously defined and X is a halogen atom, preferably chlorine.

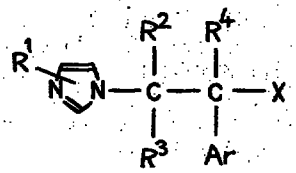
Suitable solvents for the aralkylation are the aromatic hydrocarbons, e.g. benzene, toluene or

xylene; ethers, e.g. tetrahydrofuran or 1,2-dimethoxyethane; or dimethylformamide. Tetrahydrofuran is a preferred solvent. The reaction may be performed at a temperature between 0°C and the reflux temperature of the solvent and may take from 1 to 24 hours depending on the temperature and the particular nature of the solvent and reactants employed. The product is conveniently isolated by adding water to the reaction mixture and extracting with ether. The product may then be purified as the free base or converted to a salt, e.g. the hydrochloride, and purified by recrystallisation.

The compounds of formula (I) may also be prepared by the aralkylation of a compound of formula:—

$$HZ—(CH_2)_n—Y \qquad (IV)$$

wherein Z, n and Y are as previously defined. Such a reaction comprises converting the alcohol or thiol of formula (IV) to its alkali metal derivative by treatment with a strong base, such as an alkali metal amide or hydride and reacting with an appropriate 1 - (β - haloaryl - ethyl)imidazole derivative of the formula.—



(V)

wherein R^1 to R^4 and Ar are as previously defined and X is a halogen atom, preferably chlorine.

Suitable solvents for the aralkylation are aromatic hydrocarbons, e.g. benzene, toluene or xylene; or ethers, e.g. tetrahydrofuran or 1,2-dimethoxyethane; or dimethylformamide. Tetrahydrofuran is a preferred solvent. The reaction may be performed at a temperature between 0°C and the reflux temperature of the solvent and may take from 1 to 24 hours depending on the particular nature of the solvent and reactants employed. We have found, however, that in the case of the thiols of formula (IV) the reaction is generally complete within 3 hours at room temperature when performed in tetrahydrofuran. The product may be isolated as the free base or a salt as previously described.

The starting alcohols of formula II where Z is O are known compounds described in British Patent specification No. 1244530. The starting halides of formula (V) are described in United States Patent specification No. 3679697. The halides of formula (III) and the compounds of formula (IV) are generally known compounds readily accessible or they may be prepared by conventional methods. Thus, for example, the thenyl halides of formula (III) (when Y is a thiophene ring and n is 1) are prepared, according to literature methods, by reaction of a methyl-thiophene derivative with N-bromosuccinimide, or by chloromethylation of thiophene or an appropriate halothiophene with formaldehyde and concentrated hydrochloric acid. The thiols of formula (IV) (where Z is S) may be prepared from the halides of formula (III) by reaction with thiourea followed by hydrolysis of the intermediate thiouronium derivative by refluxing with 10% sodium hydroxide solution. Thiols of formula (II) where Z is S may also be prepared by known methods, for example they may be prepared from the chloro compounds of formula (V) by reaction with thiourea followed by hydrolysis of the resulting thiouronium derivative.

The compounds of the invention exist in D- and L- optically active isomeric forms and the invention includes these forms as well as the racemic mixtures. The racemic products may be resolved by well known techniques, for example by fractional crystallisation of an addition salt formed with an optically active acid.

Pharmaceutically acceptable acid addition salts of the compounds of the invention are those formed from acids which form non-toxic acid addition salts containing pharmaceutically-acceptable anions, such as the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate and *p* - toluenesulphonate salts.

The compounds of the invention and their pharmaceutically acceptable acid addition salts are anti-fungal agents, useful in combatting fungal infections in animals, including humans. For example they are useful in treating topical fungal infections in man caused by species of *Candida, Trichophyton* or *Epidermophyton*, or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They may also be used systemically in the treatment of systemic fungal infections caused by for example *Candida albicans* or *Cryptococcus neoformans.*

The *in vitro* evaluation of the anti-fungal activity of the compounds has been performed by determining the minimum inhibitory concentration (m.i.c.) of the test compounds in a suitable medium at which growth of the particular micro-organism fails to occur. In practice a series of agar plates, each having the test compound incorporated at a particular concentration are inoculated with a standard culture of *Candida albicans* and each plate is then incubated for 24 hours at 37°C. The plates are then examined for the presence or absence of growth of the fungus and the appropriate m.i.c. value is noted. Other Micro-organisms used in such tests have included *Cryptococcus neoformans, Aspergillus fumigatus, Trichophyton rubrum, Epidermophyton*

floccosum, Coccidioides immitis, and *Torulopsis glabrata.*

The *in vivo* evaluation of the compounds has also been carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice which are inoculated with a strain of *Candida albicans.* Activity is based on the survival of a treated group of mice after the death of an untreated group of mice following 48 hours observation. The dose level at which the compound provides 50% protection against the lethal effect of the infection is noted.

For human use, the anti-fungal compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic.

For oral and parenteral administration to human patients, it is expected that the daily dosage level of the anti-fungal compounds of the invention will be comparable with that of antifungal agents currently in use, e.g. from 0.5 to 50 mg/kg (in divided doses) when administered by the parenteral routes, or from 2 to 200 mg/kg (in divided doses) when administered by the oral route. Thus tablets or capsules of the compounds can be expected to contain from 30 mg or 3 g of active compound for administration orally up to 4 times a day, while dosage units for parenteral administration will contain from 10 mg to 1 g of active compound. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with age, the weight and response of the particular patient. The above dosages are exemplary of the average host. There can, of course, be individual cases where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the anti-fungal compounds of formula (I) may be administered in the form of a suppository or pessary or they may be applied topically in the form of a cream, ointment or dusting powder. For example, they may be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they may be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The following Examples 1 to 13 are examples of the preparation of the novel compounds of formula (I) according to the invention:—

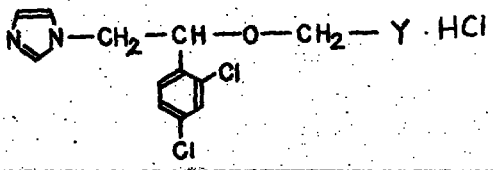
EXAMPLE 1.

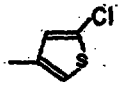
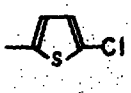
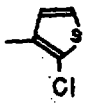
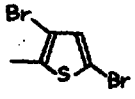
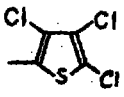
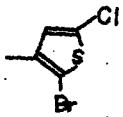
A solution of 1 - (2,4 - dichloro - phenyl)-2 - (1 - imidazolyl) ethanol (1.5 g, 5.8 mmole) dissolved in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (0.39 g, as 80% dispersion in oil, 16 mmole) in dry tetrahydrofuran (10 ml) and warmed to 70°C for 90 minutes. The mixture was cooled in ice and a solution of 2-chloromethyl-thiophene, (1.16 g, 8.8 mmole) in dry tetrahydrofuran was added. The mixture was heated at 70° for 3 hours and allowed to stir at room temperature overnight. The solvent was removed under vacuum and the residue stirred with dry ether (200 ml). The ether solution was filtered through Celite and saturated with hydrogen chloride gas to precipitate an oil which was solidified by trituration with ether and ethylacetate. The solid product was collected and recrystallised from a mixture of acetone and di-isopropyl ether to give *1 - [2,4-dichloro - β - (2 - thienylmethoxy)phenethyl]-imidazole hydrochloride* as fine white crystals (0.63 g, 31%) m.p. 153—154°C. (Found: C, 49.2; H, 3.8; N, 7.3 . $C_{16}H_{14}Cl_2N_2OS.HCl$ requires C, 49.3; H, 3.9; N, 7.2%). "CELITE is a Registered Trade Mark".

EXAMPLES 2 to 8.

The following compounds were prepared by the general method described in Example 1, starting with 1 (2,4 - dichloro - phenyl)-2- (1 - imidazolyl)ethanol and the appropriate bromo or chloromethyl-thiophene derivative. Table I shows the compounds prepared, together with their melting points and analytical data. The structures were also confirmed by IR and NMR spectroscopy.

TABLE I



Example	Y	m.p.	Analysis % (Theoretical in brackets)
2		123–124°	C, 49.3 H, 3.9 N, 7.4 (C, 41.9 H, 3.9 N, 7.1)
3		177–181°	C, 41.9 H, 2.8 N, 6.5 (C, 41.9 H, 2.9 N, 6.1)
4		164–167°	C, 45.0 H, 3.4 N, 6.9 (C, 45.3 H, 3.4 N, 6.6)
5		142–144°	C, 43.3 H, 3.4 N, 6.4 *(C, 43.4 H, 3.6 N, 6.3)
6		168–170°	C, 35.1 H, 2.4 N, 5.2 (C, 35.1 H, 2.4 N, 5.1)
7		187–190°	C, 39.1 H, 2.5 N, 5.9 (C, 39.0 H, 2.5 N, 5.7)
8		191–193°	C, 37.9 H, 2.8 N, 5.7 +(C, 37.5 H, 2.8 N, 5.5)

* Hydrate + Hemihydrate

EXAMPLE 9.

A solution of 3 - mercaptomethyl - thiophene (3.33 g, 0.019 mole) dissolved in dry tetrahydrofuran (6 ml) was added to a suspension of sodium hydride (1.7g, as an 80% dispersion in oil, 0.057 mole) in dry tetrahydrofuran (40 ml). After stirring for 1 hour at room temperature the mixture was cooled to 0°C and 1 - (β - chloro - 2,4 - dichlorophenethyl) imidazole (5.0 g, 0.16 mole) was added in portions over a period of 1 hour. The solution was stirred at 0°C for 90 minutes then diluted with water (400 ml) and extracted with ether (3 × 100 ml). The combined ether extracts were treated with HCl gas, the solvent evaporated and the residue taken up in water. The aqueous solution was washed with ether and then basified and extracted with ether. The ether extracts were dried and the solvent removed. The residue was converted to the hydrochloride salt with ethereal HCl and the product recrystallised from a mixture of methanol and di-isopropyl ether to give *1 - [2,4-dichloro - β - (3 - thienylmethylthio)phenethyl]imidazole hpdrochloride* (2.5g, 38%), m.p. 139—141°C.(Found: C, 46.8; H, 3.7; N, 6.8. $C_{16}H_{14}N_2Cl_2S_2.HCl$ requires C, 47.4; H, 3.7; N, 6.9%).

EXAMPLE 10.

In a similar manner to that described in Example 9, but using 5 - chloro - 2 - mercaptomethyl - thiophene as starting material, was prepared *1 - [2 - 4 - dichloro - β - (5-chloro - 2 - thienylmethylthio)phenethyl]-imidazolehydrochloride* m.p. 140°—143°. (Found: C, 43.4; H, 3.1; N, 6.0.

$C_{16}H_{13}N_2Cl_3S_2.HCl$

requires C, 43.8; H, 3.2; N, 6.4%).

EXAMPLE 11.

A solution of 1 - (2,4 - dichloro - phenyl)-2 - (1 - imidazolyl) ethanol (2.4 g, 9.4 mmole) in dry tetrahydrofuran (20 ml) was added to sodium hydride (0.62 g, as an 80% dispersion in oil, 0.02 mole) and warmed at 70°C for 90 minutes. The solution was cooled to 0°C and 4-chloromethylthiazole (1.5 g, 11.2 mmole), dissolved in a little dry tetrahydrofuran, was added. The mixture was stirred at 0°C for 1 hour and at room temperature for 6 hours. Further 4-chloromethylthiazole (0.25 g) was added and the stirring continued for 36 hours. The reaction mixture was then diluted with water (70 ml) and extracted several times with ether. The ether extracts were combined, dried over $MgSO_4$ and evaporated. The oily residue was taken up in dry ether (50 ml) and treated with a solution of HCl in ether. The solid precipitate was collected and recrystallised from a mixture of methanol and di-isopropyl ether to give *1 - [2,4 - dichloro - β - (4 - thiazolylmethoxy)phenethyl]imidazole hydrochloride* (1.7 g, 46%) m.p. 183—184°. (Found: C, 46.3; H, 3.7; N, 10.7. $C_{15}H_{13}N_3Cl_2OS.HCl$ requires C, 46.1; H, 3.6; N, 10.7%).

EXAMPLE 12.

In the same manner as described in Example 11, but using 2 - chloromethylthiazole as starting material, was prepared *1-[2,4 - dichloro - β - (2 - thiazolylmethoxy)-phenethyl] imidazole hydrochloride* The product was obtained as a hygroscopic gum but was shown to be homogeneous by T.L.C. and the structure confirmed by IR and NMR spectroscopy.

EXAMPLE 13.

A solution of 1 - (5 - chloro - 2 - thienyl)-2 - (1 - imidazolyl) ethanol (1.1 g, 4.8 mmole) dissolved in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (0.4 g, as 80% dispersion in oil, 16 mmole) in dry tetrahydrofuran (40 ml). After stirring for 1 hour at room temperature the mixture was cooled in ice and a solution of 2 - bromomethyl - 3 - chlorothiophene (1.0 g, 4.7 mmole) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to stir for a further 1 hour at 15°C and the solvent then removed under vacuum. The residue was extracted several times with diethyl ether and the ethereal extracts were combined and evaporated. The residue was taken up in a little diethyl ether and treated with a solution of hydrogen chloride in diethyl ether to precipitate a gum which solidified on trituration with acetone and ether. Recrystallisation from a mixture of acetone, methanol and di-isopropyl ether gave *1 - [2, - (5 - chloro - 2 - thienyl) - 2-3 - chloro - 2 - thienylmethoxy) ethyl[imidazole hydrochloride* as a white solid (0.5 g, 32%) m.p. 120—121°C. (Found: C, 41.6; H, 3.35; N, 6.9. $C_{14}H_{12}N_2Cl_2OS_2.HCl$ requires C, 42.5; H, 3.3; N, 7.1%).

EXAMPLE 14.

The following illustrate pharmaceutical compositions according to the invention for the treatment of fungal infections. Parts are by weight.

(1) *Capsule:* 71 parts of 1 - [2,4 - dichloro-β - (2 - chloro - 3 - thienylmethoxy)-phenethyl)imidazole hydrochloride are granulated with 3 parts of maize starch and 22 parts lactose and then a further 3 parts of maize starch and 1 part magnesium stearate are added and the mixture is regranulated and filled into capsules.

(2) *Cream:* 2 parts of 1 [2,4 - dichloro - β-(2 - chloro - 3 - thienylmethoxy)phenethyl]imidazole hydrochloride are dissolved in 10 parts of propylene glycol or a low molecular weight polyethylene

glycol and mixed into 88 parts of a vanishing cream base.

(3) *Dusting Powder:* 2 parts of 1 - [2,4-dichloro - β - (2 - chloro - 3 - thienylmethoxy)phenethyl]imidazole hydrochloride are ground with 9 parts of maize starch and then 89 parts of talcum powder are added and grinding continued until the required consistency is obtained.

(4) *Pessary:* 2 parts of 1 - [2,4 - dichloro-β - (2 - chloro - 3 - thienylmethoxy)-phenethyl)imidazole hydrochloride are suspended in 98 parts of a warm liquefied suppository base which is poured into moulds and allowed to cool.

The compounds prepared in Examples 1 to 13 have been tested for anti-fungal activity by the methods previously described. Table II gives m.i.c. values against *Candida albicans*. A number of compounds were also tested against several other micro-organisms. Results are given in Table III.

TABLE II

In Vitro Activity vs. Candida Albicans

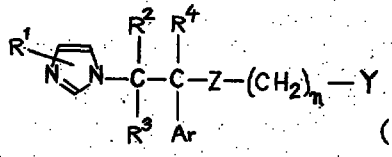
Example	m.i.c. (μg/ml)	Example	m.i.c. (μg/ml)
1	6.2	8	3.1
2	6.2	9	12.5
3	6.2	10	12.5
4	6.2	11	25
5	12.5	12	50
6	12.5	13	3.1
7	12.5		

TABLE III

Example	m.i.c. (μg/ml)				
	Trichophyton rubrum	*Epidermophyton floccosum*	*Aspergillus fumigatus*	*Cryptococcus neoformans*	*Coccidioides immitis*
1	3.2	3.2	12.5	12.5	12.5
2	0.8	3.2	6.2	3.1	3.2
4	0.8	0.8	3.1	3.1	1.6
5	3.1	6.2	12.5	0.8	12.5
11	3.1	6.2	25	<0.4	25

WHAT WE CLAIM IS:—

1. 1 - Aryl - 2 - (1 - imidazolyl)alkyl ethers and thioethers having the formula:



(I)

wherein

R^1, R^2, R^3 and R^4 are each a hydrogen atom or a lower alkyl group;

Ar is a phenyl group, which may optionally be substituted with one or more halogen atoms, lower alkyl groups or lower alkoxy groups, or a thienyl or halothienyl group;

Z is 0 or S; n is 1 or 2;

and

Y is an aromatic heterocyclic group, option-

glycol and mixed into 88 parts of a vanishing cream base.

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(4) *Pessary:* 2 parts of 1 - [2,4 - dichloro-β - (2 - chloro - 3 - thienylmethoxy)-phenethyl)imidazole hydrochloride are suspended in 98 parts of a warm liquefied suppository base which is poured into moulds and allowed to cool.

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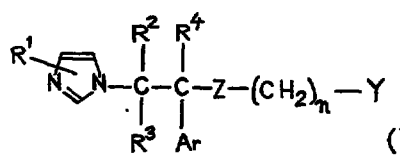
Example	m.i.c. (μg/ml)	Example	m.i.c. (μg/ml)
1	6.2	8	3.1
2	6.2	9	12.5
3	6.2	10	12.5
4	6.2	11	25
5	12.5	12	50
6	12.5	13	3.1
7	12.5		

TABLE III

Example	m.i.c. (μg/ml)				
	Trichophyton rubrum	*Epidermophyton floccosum*	*Aspergillus fumigatus*	*Cryptococcus neoformans*	*Coccidioides immitis*
1	3.2	3.2	12.5	12.5	12.5
2	0.8	3.2	6.2	3.1	3.2
4	0.8	0.8	3.1	3.1	1.6
5	3.1	6.2	12.5	0.8	12.5
11	3.1	6.2	25	<0.4	25

WHAT WE CLAIM IS:—

1. 1 - Aryl - 2 - (1 - imidazolyl)alkyl ethers and thioethers having the formula:



(I)

wherein

R^1, R^2, R^3 and R^4 are each a hydrogen atom or a lower alkyl group;

Ar is a phenyl group, which may optionally be substituted with one or more halogen atoms, lower alkyl groups or lower alkoxy groups, or a thienyl or halothienyl group;

Z is 0 or S; n is 1 or 2;

and

Y is an aromatic heterocyclic group, option-

ally substituted with one or more halogen atoms, lower alkyl groups or lower alkoxy groups

and pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 in which Ar is a phenyl or substituted phenyl group.

3. A compound as claimed in claim 1 or claim 2 in which Z is an oxygen atom.

4. A compound as claimed in claim 1 or 2 in which Z is a sulphur atom.

5. A compound as claimed in any preceding claim in which R^1, R^2, R^3 and R^4 are each a hydrogen atom.

6. A compound as claimed in any preceding claim in which Ar is a 2,4-dichlorophenyl group.

7. A compound as claimed in any preceding claim in which n is 1.

8. A compound as claimed in any preceding claim in which Y is a thienyl or halothienyl group.

9. 1 - [2,4 - dichloro - β - (3 - thienylmethoxy)phenethyl]imidazole.

10. 1 - [2,4 - dichloro - β - (5 - chloro-2 - thienylmethoxy)phenethyl]imidazole.

11. 1- [2,4 - dichloro β - (2 - chloro-3 - thienylmethoxy)phenethyl]imidazole.

12. 1 -[2,4 - dichloro - β - (2 - thienylmethoxy)phenethyl]imidazole.

13. 1 - [2,4 - dichloro - β - (2,5 - dichloro-3 - thienylmethoxy)phenethyl]imidazole.

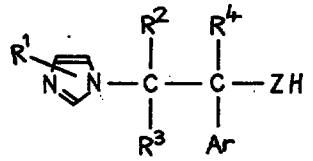
14. 1 - [2,4 - dichloro - β - (5 - chloro-2 - thienylmethylthio)phenethyl]imidazole.

15.1 - [2,4 - dichloro - β - (3 - thienylmethylthio)phenethyl]imidazole.

16. 1 - [2,4 - dichloro - β - (4 - thiazolylmethoxy)phenethyl]imidazole.

17. 1 - [2 - (5 - chloro - 2 thienyl) - 2-(3 - chloro - 2 - thienylmethoxy)ethyl]-imidazole.

18. A process for preparing a compound as claimed in claim 1, which comprises reacting the alkali metal salt of a compound of the formula:



(II)

wherein

R^1, R^2, R^3, R^4, Ar and Z are as defined in claim 1, with a compound of the formula:—

$$X—(CH_2)_n—Y$$

where

n and Y are as defined in claim 1 and X is a halogen atom and thereafter, if desired, preparing a pharmaceutically acceptable salt of the product so formed.

19. A process for the preparation of a compound as claimed in claim 1 substantially as hereinbefore described with reference to any of the Examples 1 to 13.

20. A 1 - aryl - 2 - (1 - imidazolyl)alkyl ether or thioether when prepared by the process of claim 18 or claim 19.

21. A pharmaceutical composition for the treatment of fungal infections containing as active ingredient a compound as claimed in claim 1 together with a pharmaceutically acceptable carrier.

22. A method of treating fungal infections in non-human animals which comprises administering an effective amount of a compound as claimed in any of claims 1 to 17 or 20 either alone or in the form of a pharmaceutical composition as claimed in claim 21.

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