

The PhD thesis of De Wit K. describes the implementation of an *in vitro* and *in vivo* mycological evaluation platform and activity profiling of antifungal pyrrolobenzodiazepines (PhD Thesis; University of Antwerp, Belgium; Faculty of Pharmaceutical, Biomedical and Veterinary Sciences; Department of Biomedical Sciences; 2011; 220 p.).

The antifungal compounds of the present invention or part of the compounds of the present invention are structurally different and may have improved potency, improved metabolic stability properties, improved solubility, improved plasma binding, reduced hERG channel inhibition, reduced cytochrome P450 liabilities, or improved bioavailability compared with compounds disclosed in the prior art. Preferably said compounds have a broad antifungal spectrum, and maintain adequately high therapeutic efficacy and adequately low toxicity or other side effects.

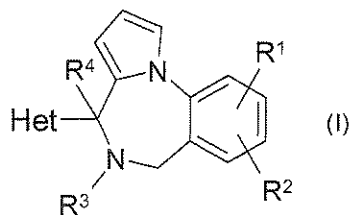
The compounds of the present invention are useful as squalene epoxidase inhibitors.

It is accordingly an object of the present invention to provide novel compounds with antifungal activity to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide useful alternative compounds.

Summary of the invention

It has been found that the compounds of the present invention are useful as antifungal compounds.

The present invention concerns novel compounds of Formula (I):



and stereoisomeric forms thereof, wherein

R¹ is hydrogen, halo, C₁₋₄alkyl or C₁₋₄alkyloxy;

R² is hydrogen, halo, C₁₋₄alkyl or C₁₋₄alkyloxy;

R³ and R⁴ are hydrogen;

or R³ and R⁴ taken together form a bond;

Het is a monocyclic or bicyclic heterocyclic radical selected from

$-(CH_2)_s-$ (c), or

$-CH=CH-CH=CH-$ (d);

wherein the bivalent radical $-R^5-R^6-$ may, where possible, be substituted with one or more substituents selected from the group consisting of halo, C_{1-4} alkyl, hydroxyl, C_{1-4} alkyloxy and oxo;

m represents 0, 1 or 2;

5 n represents 2, 3 or 4;

s represents 3, 4 or 5;

wherein radicals (d-1)-(d-11) may be substituted with one or more substituents each independently selected from the group consisting of C_{1-4} alkyloxy, halo,

C_{1-4} alkylcarbonyl, C_{1-4} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4} alkylsulphinyl, and C_{1-4} alkyl

10 optionally substituted with one or more halo substituents;

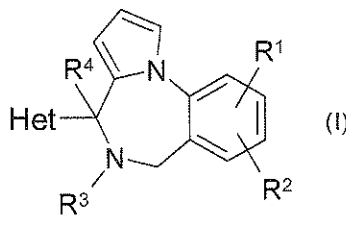
provided that radicals (d-1)-(d-11) are not substituted in the α -positions to the carbon atom of attachment;

and the pharmaceutically acceptable addition salts, and the solvates thereof;

provided that the compound is not 5,6-dihydro-4-(2-pyridinyl)-4*H*-pyrrolo[1,2-*a*][1,4]

15 benzodiazepine .HCl.

In a first aspect, there is provided a compound of formula (I)



or a stereoisomeric form thereof, wherein,

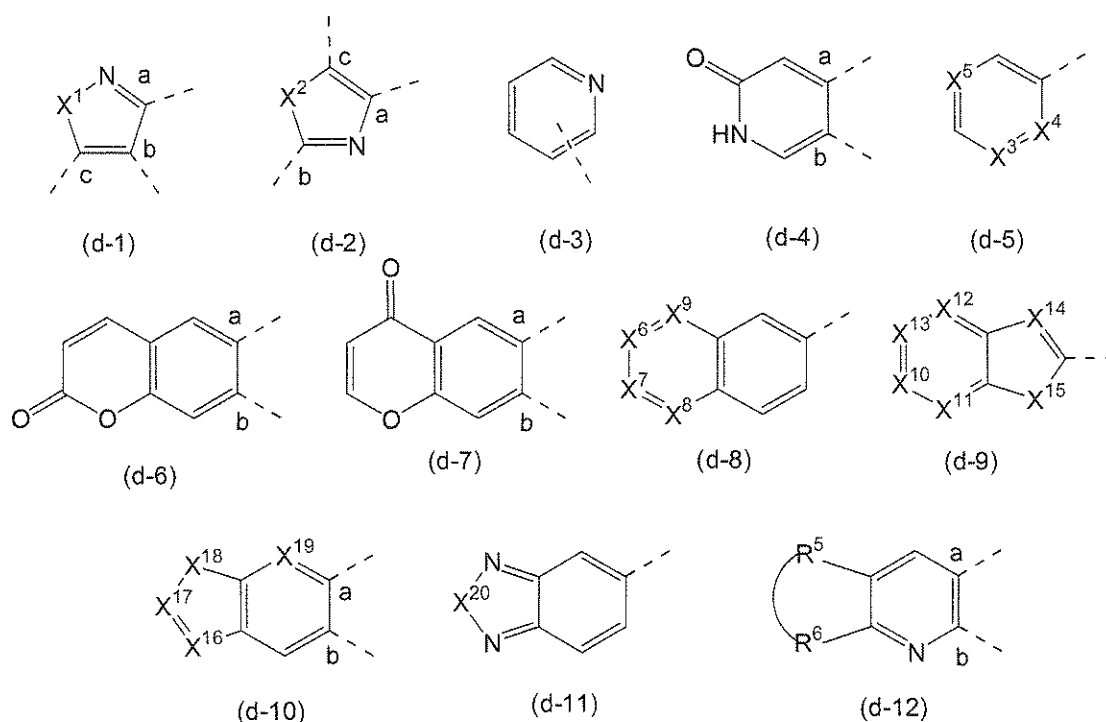
R^1 is hydrogen, halo, C_{1-4} alkyl or C_{1-4} alkyloxy;

20 R^2 is hydrogen, halo, C_{1-4} alkyl or C_{1-4} alkyloxy;

R^3 and R^4 are hydrogen;

or R^3 and R^4 taken together form a bond;

Het is a monocyclic or bicyclic heterocyclic radical selected from



(d-1) and (d-2) are attached to the remainder of the molecule with a bond in position a, b or c;

(d-4), (d-6), (d-7), (d-10) and (d-12) are attached to the remainder of the molecule with a bond in position a or b;

X^1 is O, S or NH;

X^2 is O or S;

X^3 , X^4 and X^5 each independently are CH or N; provided that exactly two of X^3 , X^4 and X^5 are N, the other being CH;

X^6 , X^7 , X^8 and X^9 each independently are CH or N; provided that one or two of X^6 , X^7 , X^8 and X^9 are N, the other being CH;

X^{10} , X^{11} , X^{12} and X^{13} each independently are CH or N; provided that maximum one of X^{10} , X^{11} , X^{12} and X^{13} is N, the other being CH;

X^{14} is CH or N;

X^{15} is NH, O or S;

X^{16} is CH or N;

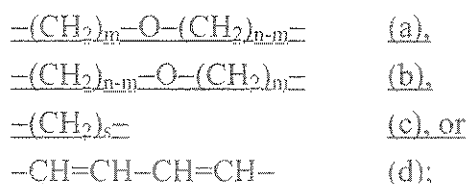
X^{17} is CH or N;

X^{18} is NH, S or O;

X^{19} is CH or N;

X^{20} is NH or S;

R^5 and R^6 taken together form a bivalent radical $-R^5-R^6-$, having formula:



wherein the bivalent radical $-R^5-R^6-$ may, where possible, be substituted with one or more substituents selected from the group consisting of halo, C_{1-4} alkyl, hydroxyl,

C_{1-4} alkyloxy and oxo;

m represents 0, 1 or 2;

5 n represents 2, 3 or 4;

s represents 3, 4 or 5;

wherein radicals (d-1)-(d-11) may be substituted with one or more substituents each independently selected from the group consisting of C_{1-4} alkyloxy, halo,

C_{1-4} alkylcarbonyl, C_{1-4} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4} alkylsulphinyl, and C_{1-4} alkyl

10 optionally substituted with one or more halo substituents;

provided that radicals (d-1)-(d-11) are not substituted in the α -positions to the carbon atom of attachment;

or a pharmaceutically acceptable addition salt or a solvate thereof;

provided that the compound is not 5,6-dihydro-4-(2-pyridinyl)-4H-pyrrolo[1,2-a][1,4]

15 benzodiazepine .HCl, 5,6-dihydro-4-(2-pyridinyl)-4H-pyrrolo[1,2-a][1,4]

benzodiazepine or 5,6-dihydro-4-(3-pyridinyl)-4H-pyrrolo[1,2-a][1,4]

benzodiazepine.

The present ~~invention~~disclosure also concerns methods for the preparation of compounds of Formula (I) and pharmaceutical compositions comprising them.

20 In a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined above.

The present compounds are useful agents for combating fungi *in vivo*.

25 In a third aspect, there is provided a compound as defined above for use as a medicament.

In a fourth aspect, there is provided a compound as defined above for use in the treatment or prevention of a fungal infection.

30 The novel compounds described in the present ~~invention~~disclosure may be useful in the treatment or prevention of infections caused by dermatophytes, systemic fungal infections and onychomycosis; in particular infections caused by dermatophytes.

The novel compounds described in the present inventiondisclosure may be active against a wide variety of fungi, such as *Candida* spp., e.g. *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida kefyr*, *Candida tropicalis*; *Aspergillus* spp., e.g. *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*; *Cryptococcus* spp., e.g. *Cryptococcus neoformans*; *Sporothrix schenckii*; *Epidermophyton floccosum*; *Microsporum* spp., e.g. *Microsporum canis*, *Microsporum gypseum*; *Trichophyton* spp., e.g. *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton quinckeanum*, *Trichophyton tonsurans*, *Trichophyton verrucosum*, *Trichophyton violaceum*, *Trichophyton interdigitale*, *Trichophyton soudanense*; *Fusarium* spp., e.g. *Fusarium solani*, *Fusarium oxysporum*, *Fusarium proliferatum*, *Fusarium verticillioides*; *Rhizomucor* spp., e.g. *Rhizomucor miehei*, *Rhizomucor pusillus*; *Mucor circinelloides*; *Rhizopus* spp., e.g. *Rhizopus oryzae*, *Rhizopus microspores*; *Malassezia furfur*; *Acremonium*

spp.; *Paecilomyces*; *Scopulariopsis*; *Arthrographis* spp.; *Scytalidium*; *Scedosporium* spp., e.g. *Scedosporium apiospermum*, *Scedosporium prolificans*; *Trichoderma* spp.; *Penicillium* spp.; *Penicillium marneffei*; *Blastoschizomyces*.

In view of the aforementioned pharmacology of the present compounds, it follows that they are suitable for use as a medicament.

The inventiondisclosure also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable addition salts and the solvates thereof, for use in the treatment or prevention of fungal infections.

One advantage of the compounds or a part of the compounds of the present inventiondisclosure may lie in their enhanced bioavailability, improved metabolic stability properties, improved PK properties, reduced hERG channel inhibition, or reduced cytochrome P450 liabilities compared with the compounds disclosed in the prior art.

The present inventiondisclosure will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

Whenever the term “substituted” is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 4 hydrogens, preferably from 1 to 3 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

The term “halo” or “halogen” as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.

The term “C₁₋₄alkyl” as a group or part of a group (e.g. in C₁₋₄alkylcarbonyl, C₁₋₄alkylthio, C₁₋₄alkylsulphonyl, C₁₋₄alkylsulphinyl) refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 4. C₁₋₄alkyl groups comprise

- X^6 , X^7 , X^8 and X^9 each independently are CH or N; provided that one or two of X^6 , X^7 , X^8 and X^9 are N, the other being CH;
 X^{10} , X^{11} , X^{12} and X^{13} each independently are CH or N; provided that maximum one of X^{10} , X^{11} , X^{12} and X^{13} is N, the other being CH;
- 5 X^{14} is CH or N;
 X^{15} is NH, O or S;
 X^{16} is CH or N;
 X^{17} is CH or N;
 X^{18} is NH, S or O;
- 10 X^{19} is CH or N;
 X^{20} is NH or S;
 R^5 and R^6 taken together form a bivalent radical $-R^5-R^6-$, having formula:
- $-(CH_2)_m-O-(CH_2)_n-$ (a),
 $-(CH_2)_n-O-(CH_2)_m-$ (b),
 $-(CH_2)_s-$ (c), or
 $-CH=CH-CH=CH-$ (d);
- wherein the bivalent radical $-R^5-R^6-$ may, where possible, be substituted with one or more substituents selected from the group consisting of halo, C_{1-4} alkyl, hydroxyl,
- 15 C_{1-4} alkoxy and oxo;
m represents 0, 1 or 2;
n represents 2, 3 or 4;
s represents 3, 4 or 5;
- wherein radicals (d-1)-(d-11) may be substituted with one or more substituents each
- 20 independently selected from the group consisting of C_{1-4} alkoxy, halo, C_{1-4} alkylcarbonyl, C_{1-4} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4} alkylsulphinyl, and C_{1-4} alkyl optionally substituted with one or more halo substituents;
provided that radicals (d-1)-(d-11) are not substituted in the α -positions to the carbon atom of attachment;
- 25 or a pharmaceutically acceptable addition salt or a solvate thereof;
provided that the compound is not 5,6-dihydro-4-(2-pyridinyl)-4H-pyrrolo[1,2-a][1,4]benzodiazepine .HCl, 5,6-dihydro-4-(2-pyridinyl)-4H-pyrrolo[1,2-a][1,4]benzodiazepine or 5,6-dihydro-4-(3-pyridinyl)-4H-pyrrolo[1,2-a][1,4]benzodiazepine.
- 30
2. The compound according to claim 1 or a stereoisomeric form thereof, wherein,
 X^6 , X^7 , X^8 and X^9 each independently are CH or N; provided that exactly one of X^6 , X^7 , X^8 and X^9 is N, the other being CH;
 X^{15} is O or S;
- 35 R^5 and R^6 taken together form a bivalent radical $-R^5-R^6-$, having formula: