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(71) Applicant: **MERZ PHARMA GMBH & CO. KGAA**
[DE/DE]; Eckenheimer Landstraße 100, 60318
Frankfurt/Main (DE).

(72) Inventors: **POOTH, Rainer**; Dachbergstr. 46A, 65812
Bad Soden/Taunus (DE). **BARG, Heiko**; Siegfriedstr. 25,
69469 Weinheim (DE). **ABTS, Harry Frank**; Kurmain-

zer-Str. 14, 61440 Oberursel (DE). **KIEHM, Kevin**; Land-
graf-Philipp-Str. 44, 60431 Frankfurt (DE).

(74) Agent: **MICHALSKI HÜTTERMANN & PARTNER**
PATENTANWÄLTE; Neuer Zollhof 2, 40221 Düsseldorf
(DE).

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(54) Title: USE OF AZOLE ANTIFUNGALS FOR THE TREATMENT OF ACTINIC KERATOSIS

(57) Abstract: Use of azole antifungals for the treatment of
actinic keratosis.

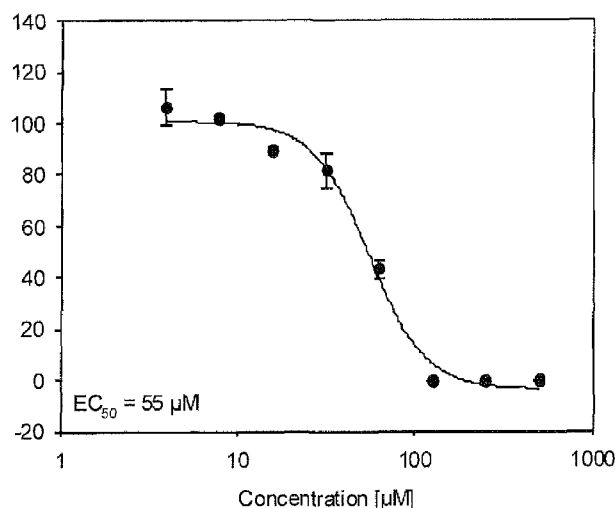
Ketoconazole_48h Resazurine

Fig. 1



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GW, ML, MR, NE, SN, TD, TG).

Use of azole antifungals for the treatment of actinic keratosis

5 The present invention relates to the use of azole antifungals for the treatment of actinic keratosis.

10 In general, actinic keratosis (also called "solar keratosis" and "senile keratosis", AK) is a premalignant condition of thick, scaly, or crusty patches of skin consisting of dysplastic keratinocytic lesions. AK is one of the most common conditions treated by dermatologists. It is more common in fair-skinned people. And most important it is associated with those who are frequently exposed to the sun, as it is usually accompanied by solar damage. It is generally accepted that these lesions can progress to squamous cell carcinoma (SCC). Concerning the rate of this transformation there is a controversy in the literature with annual rates of transformation described in the range of 0.1% - 20%. Nevertheless there is
15 no doubt that these pre-cancerous lesions should be treated in order to prevent manifestation of malignant tumors. In addition lesions are in general treated also for cosmetic purposes and to provide relief from symptoms, such as tenderness or itch.

20 When skin is exposed to the sun constantly, thick, scaly, or crusty bumps may appear. The scaly or crusty part of the bump is dry and rough. The growths start out as flat scaly areas, and later grow into a tough, wart-like area.

25 In addition to chronic UV-exposure also infections with HPV has been implicated in the aetiology of AK.

30 An actinic keratosis site commonly ranges between 2 and 6 millimeters in size, and can be dark or light, tan, pink, red, a combination of all these, or have the same pigment as the surrounding skin. It typically appears on any sun-exposed area, such as the face, ears, neck, scalp, chest, backs of hands, forearms, or lips.

An efficient treatment that can be used for focal (lesional) but also for treatment of larger areas of affected skin and eliminate obvious AK lesions as well as clinically non visible pre-lesions would be beneficial for the patient.

Therefore, it is an object of the present invention to provide alternative treatments for actinic keratosis with improved patient convenience.

This object is solved by Claim 1 of the present invention. Accordingly, the use of azole antifungals for the treatment of actinic keratosis is provided.

Surprisingly it has been found that these compounds can be used for the treatment of actinic keratosis. Without being bound to any theory the inventors believe that this due to the keratinolytic activity of the claimed compounds.

This profound keratinolytic activity is responsible for the primary curing effect in AK.

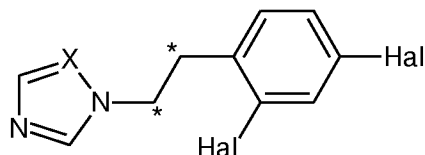
According to a preferred embodiment of the present invention, the azole antifungals comprise an imidazole or triazole moiety.

The term "moiety" in the sense of the present invention especially means and/or includes that such a chemical structure is part of the molecule; however the moiety may be a substructure of the molecule.

Preferably the imidazole or triazole moiety is N-substituted.

More preferred the imidazole or triazole moiety is N-substituted in that way that in β -position a substituted or unsubstituted benzene ring is located.

Said benzene ring is preferably (di-)halogenated in 2- and/or 4-position (the chemical link to the imidazole or triazole moiety being the 1-position). Thus the azole antifungals preferably comprise a moiety of the following structure:



with X being CH or N. Preferably the halogens are chlorides and/or fluorides.

As indicated by the "*" either the α -carbon or the β -carbon to the imidazole or triazole may be further substituted; however it is preferred that the α -carbon is unsubstituted (i.e. there is a CH_2 -group), whereas the β -carbon is further substituted. "Substituted" in this context means especially that one or two more chemical moieties may be present by one or two single bonds or one double bond.

It should be noted that the α -carbon and the β -carbon to the imidazole or triazole may be further substituted in that way that they form a double bond; this is actually a further embodiment of the present invention.

Alternatively and also according to a preferred embodiment of the present invention, the imidazole or triazole moiety is N-substituted in that way that in α -position one or two substituted or unsubstituted benzene rings are located.

According to a preferred embodiment of the present invention, the pK of the azole antifungals is between ≥ 6.5 and ≤ 8.5 , preferably between ≥ 7.0 and ≤ 8 . This has been shown in practice to increase the activity against AK.

Generic group definition: Throughout the description and claims generic groups have been used, for example alkyl, alkoxy, aryl. Unless otherwise specified the following are preferred groups that may be applied to generic groups found within compounds disclosed herein:

alkyl: linear and branched C1-C8-alkyl,

long-chain alkyl: linear and branched C5-C20 alkyl

alkenyl: C2-C6-alkenyl,

cycloalkyl: C3-C8-cycloalkyl,

alkoxy: C1-C6-alkoxy,

long-chain alkoxy: linear and branched C5-C20 alkoxy

aryl: selected from homoaromatic compounds having a molecular weight under 300,

halogen: selected from the group consisting of: F; Cl; Br and I,

halogenalkyl: selected from the group consisting of mono, di, tri-, poly and perhalogenated linear and branched C1-C8-alkyl

5

Unless otherwise specified the following are more preferred group restrictions that may be applied to groups found within compounds disclosed herein:

10

alkyl: linear and branched C1-C6-alkyl, more preferred methyl, ethyl, propyl, isopropyl, butyl, isobutyl

long-chain alkyl: linear and branched C8-C15 alkyl, preferably linear C10-C12 alkyl

15

alkenyl: C3-C6-alkenyl,

cycloalkyl: C6-C8-cycloalkyl,

alkoxy: C1-C4-alkoxy,

20

long-chain alkoxy: linear and branched C5-C10 alkoxy, preferably linear C6-C8 alkoxy

aryl: selected from group consisting of: phenyl; biphenyl; naphthalenyl; anthracenyl; and phenanthrenyl,

25

halogen: selected from the group consisting of: F and Cl,

30

According to a preferred embodiment of the present invention the azole antifungals are selected out of the group comprising ketoconazole, tioconazole, miconazole, sulconazole, oxiconazole, posaconazole, clotrimazole, econazole, bifonazole, butoconazole, omoconazole, fenticonazole, isoconazole, fluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole, albaconazole or mixtures thereof.

Ketoconazole refers to 1-[4-(4-[[[(2R,4S)-2-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one.

35

Tioconazole refers to (RS)-1-[2-[(2-Chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole.

5 Miconazole refers to (RS)-1-(2-(2,4-Dichlorobenzoyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole.

Sulconazole refers to 1-(2-[[4-(4-chlorophenyl)methyl]sulfanyl]-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole.

10 Oxiconazole refers to (E)-[1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethylidene][(2,4-dichlorophenyl)methoxy]amine.

15 Posaconazole refers to 4-(4-(4-(4-(((3r,5r)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-yl)methyl)oxolan-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2s,3s)-2-hydroxypentan-3-yl)-1,2,4-triazol-3-one.

Clotrimazole refers to 1-[(2-chlorophenyl)(diphenyl)methyl]-1H-imidazole.

20 Econazole refers to (RS)-1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole.

Bifonazole refers to (RS)-1-[phenyl(4-phenylphenyl)methyl]-1H-imidazole.

25 Butoconazole refers to 1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenyl)sulfanylbutyl]imidazole.

Omoconazole refers to 1-[(Z)-2-[2-(4-chlorophenoxy)ethoxy]-2-(2,4-dichlorophenyl)-1-methylvinyl]-1H-imidazole.

30 Fenticonazole refers to 1-[2-(2,4-dichlorophenyl)-2-[[4-(phenylsulfanyl)phenyl]methoxy]ethyl]-1H-imidazole.

Isoconazole refers to (RS)-1-[2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole.

35 Fluconazole refers to 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol.

Itraconazole refers to (2R,4S)-rel-1-(butan-2-yl)-4-{4-[4-(4-[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy)phenyl)piperazin-1-yl]phenyl}-4,5-dihydro-1H-1,2,4-triazol-5-one.

5

Isavuconazole refers to 4-{2-[(1R,2R)-(2,5-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-1,3-thiazol-4-yl}benzonitrile.

10

Ravuconazole refers to 4-[2-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl]benzonitrile.

15

Posaconazole refers to 4-(4-(4-(4-(((3r,5r)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2s,3s)-2-hydroxypentan-3-yl)-1,2,4-triazol-3-one.

Voriconazole refers to (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

20

Terconazole refers to 1-[4-[(2S,4S)-2-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-propan-2-yl-piperazine.

Albaconazole refers to 7-chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one.

Application of a formulation comprising the azole antifungals of the present invention can be carried out by topical application or any form of injection, in particular by epicutaneous injection.

The azole antifungals according to the present invention can be applied topically. Examples for a topic application of a formulation comprising a molecule according to the present invention include a cream, a patch, a salve, a gel, a powder, a dressing, ointment, microemulsions, liposomes, nanoparticles, semi-solid-nanoparticles without or with the use of iontophoresis or other transdermal systems.

Preferably the concentration of the azole antifungals according to the present invention is from about $\geq 0.0001\%$ to about $\leq 20\%$ (wt/wt), preferred from about $\geq 0.001\%$ to about $\leq$

15%, more preferred from about $\geq 0.01\%$ to about $\leq 10\%$, yet more preferred about $\geq 0.1\%$ to about $\leq 10\%$ and most preferred about $\geq 2\%$ to about $\leq 5\%$.

Preferably the concentration of the azole antifungals according to the present invention is
5 from about $\geq 0.0001\%$ to about $\leq 0.1\%$ (wt/wt), preferred from about $\geq 0.01\%$ to about $\leq 10\%$, more preferred from about $\geq 0.1\%$ to about $\leq 5\%$, yet more preferred about $\geq 0.05\%$ to about $\leq 1\%$ and most preferred about $\geq 0.2\%$ to about $\leq 2\%$.

Alternatively, the azole antifungals according to the present invention can be applied by
10 epicutaneous injection. Examples for epicutaneous injection include aqueous solutions, suspensions, oily solutions, emulsions, microemulsions, liposomes, microspheres, nanoparticles and implants. The advantage of cutaneous injections (preferentially into actinic lesion) is the rapid onset of action and that the cytolytic effect is restricted to the targeted tissue. In general by local dermal application the systemic availability of
15 compounds over time is reduced, since drug absorption from epidermal tissue is slow and sustained.

Preferably, each topical application or injection unit of the formulation has a distinct dose of the azole antifungals according to the present invention. This dose can reach from about $\geq$
20 2.5 nMol to about $\leq 50\text{ mMol}$, preferred from about $\geq 10\text{ }\mu\text{Mol}$ to about $\leq 10\text{ mMol}$, preferred from about $\geq 100\text{ }\mu\text{Mol}$ to about $\leq 1\text{ mMol}$, per volume of one application.

In another embodiment this dose can reach from about $\geq 2.5\text{ nMol}$ to about $\leq 10\text{ }\mu\text{Mol}$, preferred from about $\geq 10\text{ }\mu\text{Mol}$ to about $\leq 100\text{ }\mu\text{Mol}$, preferred from about $\geq$
25 $100\text{ }\mu\text{Mol}$ to about $\leq 1000\text{ }\mu\text{Mol}$, preferred from about $\geq 1000\text{ }\mu\text{Mol}$ to about $\leq 50\text{ mMol}$, preferred per volume of one application.

In case that the application occurs via injection, preferably one injection shot is sized from about 0.10 ml of the formulation to about 5.0 ml , more preferable between 0.5 and 2 ml ,
30 preferably around 1 ml .

In case that the application occurs via topical application, preferably per cm^2 treated area about $0.1 - 5\text{ mg}$ of the formulation, more preferable between $0.5 - 2\text{ mg}$, preferably around 1 mg is applied.

35 The present invention furthermore relates to a formulation comprising azole antifungals for the treatment of actinic keratosis.

The present invention furthermore relates to process, comprising: administering azole antifungals to a human in an amount effective for treating actinic keratosis

5 In an additional embodiment the claimed molecules are combined with an additional keratolytic agent in order to support the therapeutic effect. The keratolytic agent could simply be a chemical peel like compound like salicylic-acid ore could have a more efficient keratino-cytolic activity like retinoids.

10 Additional details, characteristics and advantages of the object of the invention are disclosed in the subclaims and the following description of the respective figures and examples.

Fig. 1 is a diagram showing the relative viability vs. the concentration for the compound
15 according to Example 1 of the present invention on NHEK-cells

Fig. 2 is a diagram showing the relative viability vs. the concentration for the compound according to Example 2 of the present invention on NHEK-1-cells

20 Fig. 3 is a diagram showing the relative viability vs. the concentration for the compound according to Example 3 of the present invention on NHEK-cells

Fig. 4 is a diagram showing the relative viability vs. the concentration for the compound according to Example 4 of the present invention on NHEK-cells
25

Fig. 5 is a diagram showing the relative viability vs. the concentration for the compound according to Example 5 of the present invention on NHEK-cells

Fig. 6 is a diagram showing the relative viability vs. the concentration for the compound
30 according to Example 6 of the present invention on NHEK-cells

Fig. 7 is a diagram showing the relative viability vs. the concentration for the compound according to Example 7 of the present invention on NHEK-cells

35 Fig. 8 is a diagram showing the relative viability vs. the concentration for the compound according to Example 8 of the present invention on NHEK-cells

EXAMPLE I:

Example 1 refers to Ketoconazole, whose structure is given above.

By using primary, normal human epidermal keratinocytes (NHEK, Fig. 1) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of ketoconazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 1 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

EXAMPLE II

Example 2 refers to Tioconazole, whose structure is given above.

By using primary, normal human epidermal keratinocytes (NHEK, Fig. 2) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of tioconazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 2 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

EXAMPLE III:

Example 3 refers to Miconazole, whose structure is given above.

By using primary, normal human epidermal keratinocytes (NHEK, Fig. 3) the cytolytic potential of the drug compound was investigated.

5 The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of miconazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

10 From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 3 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

EXAMPLE IV:

15 Example 4 refers to clotrimazole, whose structure is given above.

By using primary, normal human epidermal keratinocytes (NHEK, Fig. 4) the cytolytic potential of the drug compound was investigated.

20 The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of clotrimazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

25 From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 4 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

EXAMPLE V:

30 Example 5 refers to econazole, whose structure is given above.

By using primary, normal human epidermal keratinocytes (NHEK, Fig. 5) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of econazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

5 From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 5 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

10 EXAMPLE VI:

Example 6 refers to oxiconazole, whose structure is given above.

15 By using primary, normal human epidermal keratinocytes (NHEK, Fig. 6) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of oxiconazole were investigated. Viability of the cells was plotted against the different concentration of test compound.

20 From the resulting sigmoid-curve the IC₅₀ value for the cytolytic effect was determined and given in the respective figure. Fig. 6 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

25 EXAMPLE VII:

Example 7 refers to sulconazole, whose structure is given above.

30 By using primary, normal human epidermal keratinocytes (NHEK, Fig. 7) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of sulconazole were investigated.

35 Viability of the cells was plotted against the different concentration of test compound.

From the resulting sigmoid-curve the IC50 value for the cytolytic effect was determined and given in the respective figure. Fig. 7 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

5

EXAMPLE VIII:

Example 8 refers to posaconazole, whose structure is given above.

10 By using primary, normal human epidermal keratinocytes (NHEK, Fig. 8) the cytolytic potential of the drug compound was investigated.

The viability of the cells was monitored by their metabolic activity using the Resazurin - assay. Eight different concentrations (up to 1 mM) of posaconazole were investigated.

15 Viability of the cells was plotted against the different concentration of test compound.

From the resulting sigmoid-curve the IC50 value for the cytolytic effect was determined and given in the respective figure. Fig. 8 depicts the relative viability of NHEK-cells vs. the concentration of test-compound using metabolic activity as read-out. The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

20

FURTHER EXAMPLES AND DATA

25 Table I shows the IC50 value for the cytolytic effect using NHEK cells for the some of the substances above and some further inventive compounds I:

TABLE I

No	Compound	IC 50 [μ M] NHEK	
1	Ketokonazole	55,00	
2	Tioconazole	5,00	
3	Miconazole	3,00	
4	Coltrimazole	6,00	
5	Econazole	4,00	
6	Oxiconazole	4,00	
7	Sulconazole	5,00	
8	Posaconazole	100,00	

The obtained data show a clear negative-impact of suggested drug compound on the viability of the cells.

- 5 The particular combinations of elements and features in the above detailed embodiments are exemplary only; the interchanging and substitution of these teachings with other teachings in this and the patents/applications incorporated by reference are also expressly contemplated. As those skilled in the art will recognize, variations, modifications, and other implementations of what is described herein can occur to those of ordinary skill in the art
- 10 without departing from the spirit and the scope of the invention as claimed. Accordingly, the foregoing description is by way of example only and is not intended as limiting. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these
- 15 measured cannot be used to advantage. The invention's scope is defined in the following claims and the equivalents thereto. Furthermore, reference signs used in the description and claims do not limit the scope of the invention as claimed.

Claims

1. Use of azole antifungals for the treatment of actinic keratosis
2. Use according to claim 1, whereby the azole antifungals comprise an imidazole or triazole moiety.
3. Use according to claim 1 or 2, whereby the azole antifungals comprise an N-substituted imidazole or triazole moiety.
4. Use according to any of the claims 1 to 3, whereby the azole antifungals comprise an N-substituted imidazole or triazole moiety in that way that in β -position to the imidazole or triazole moiety a substituted or unsubstituted benzene ring is located.
5. Use according to any of the claims 1 to 4, whereby the azole antifungals comprise an N-substituted imidazole or triazole moiety in that way that in β -position to the imidazole or triazole moiety a substituted or unsubstituted benzene ring is located which is (di-)halogenated in 2- and/or 4-position.
6. Use according to any of the claims 1 to 5, whereby the azole antifungals comprise an N-substituted imidazole or triazole moiety in that way that in α -position one or two substituted or unsubstituted benzene rings are located
7. Use according to any of the claims 1 to 6, whereby the azole antifungals are applied topically or in form of an injection
8. Use according to any of the claims 1 to 7, whereby the dose of azole antifungals according to the present invention per one application is between from about 3 μ Mol to about 50 mMol.

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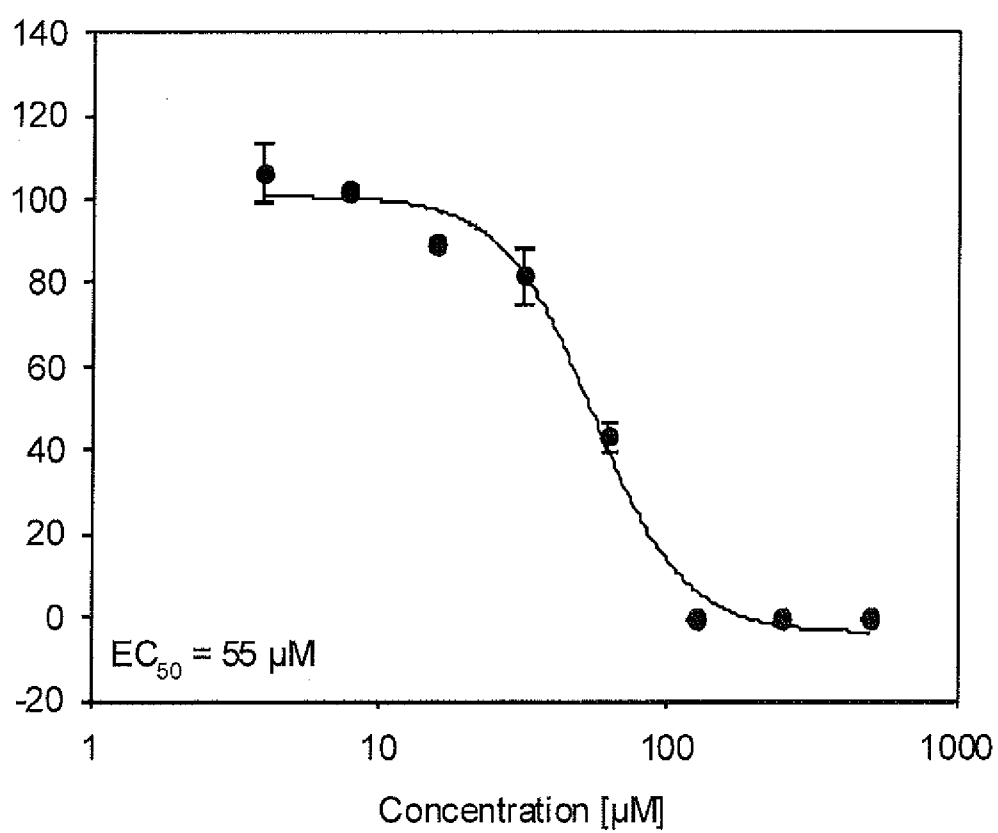
Ketoconazole_48h Resazurine

Fig. 1

2 / 8

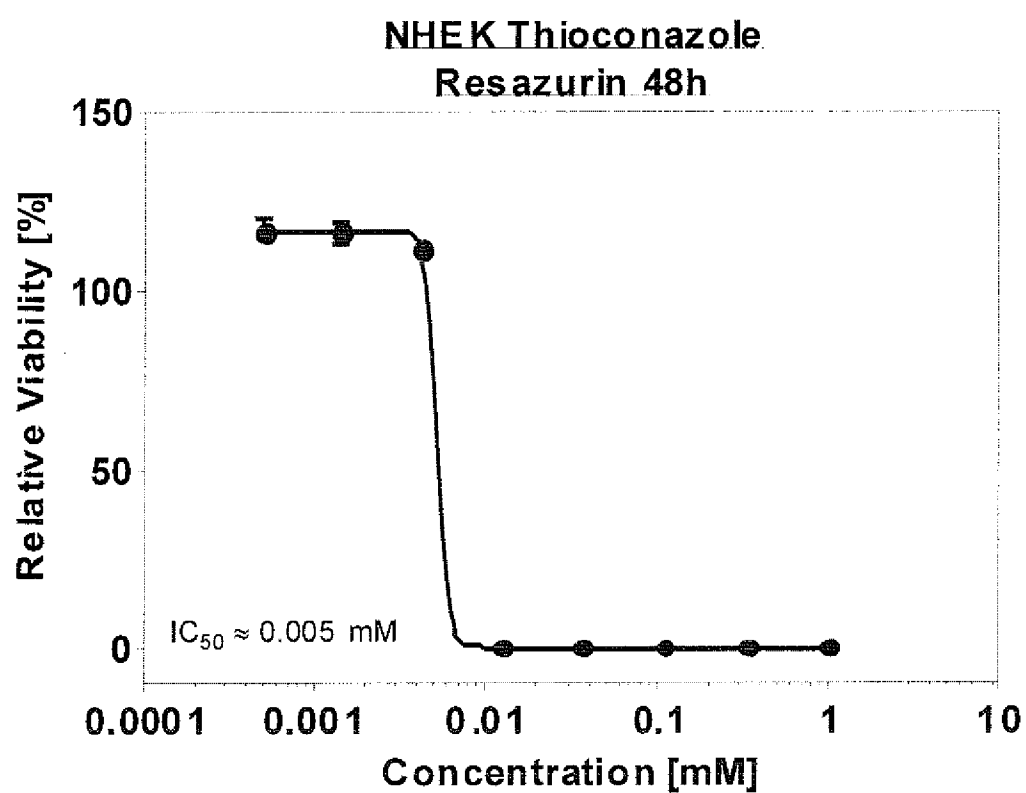


Fig. 2

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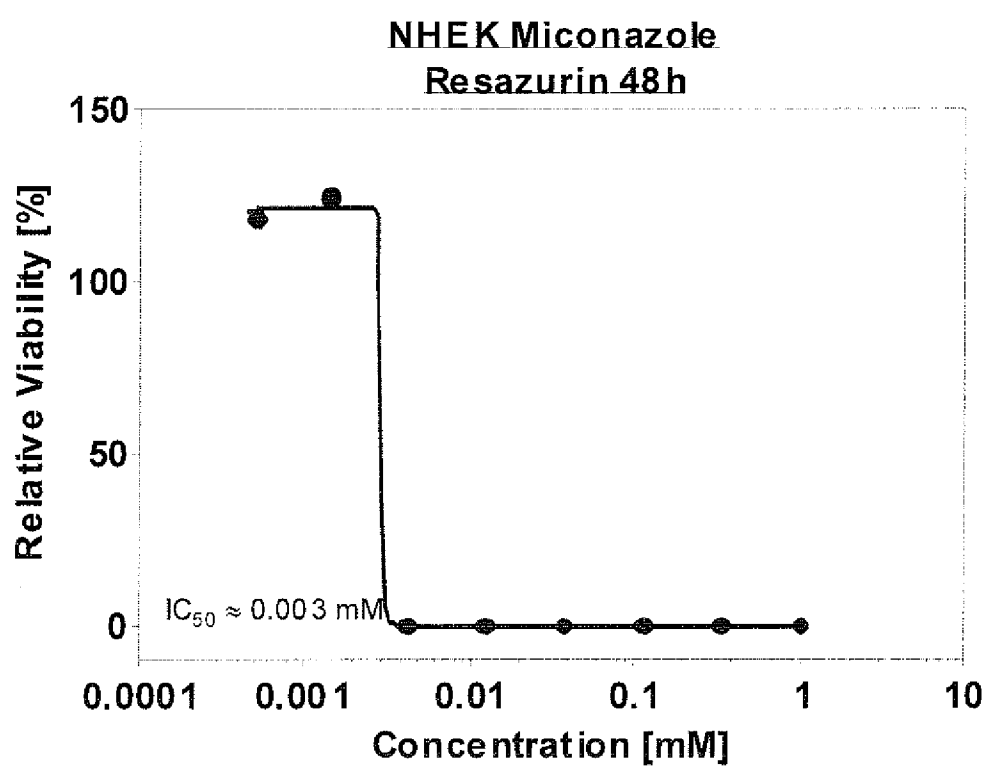


Fig. 3

4 / 8

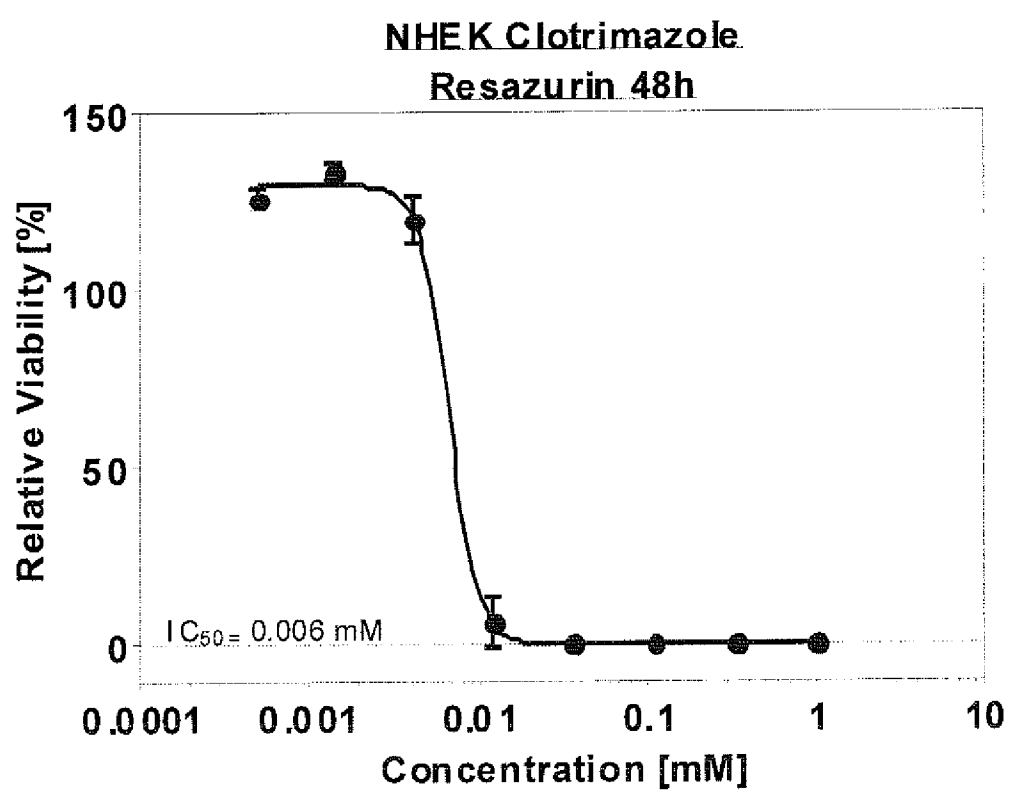


Fig. 4

5 / 8

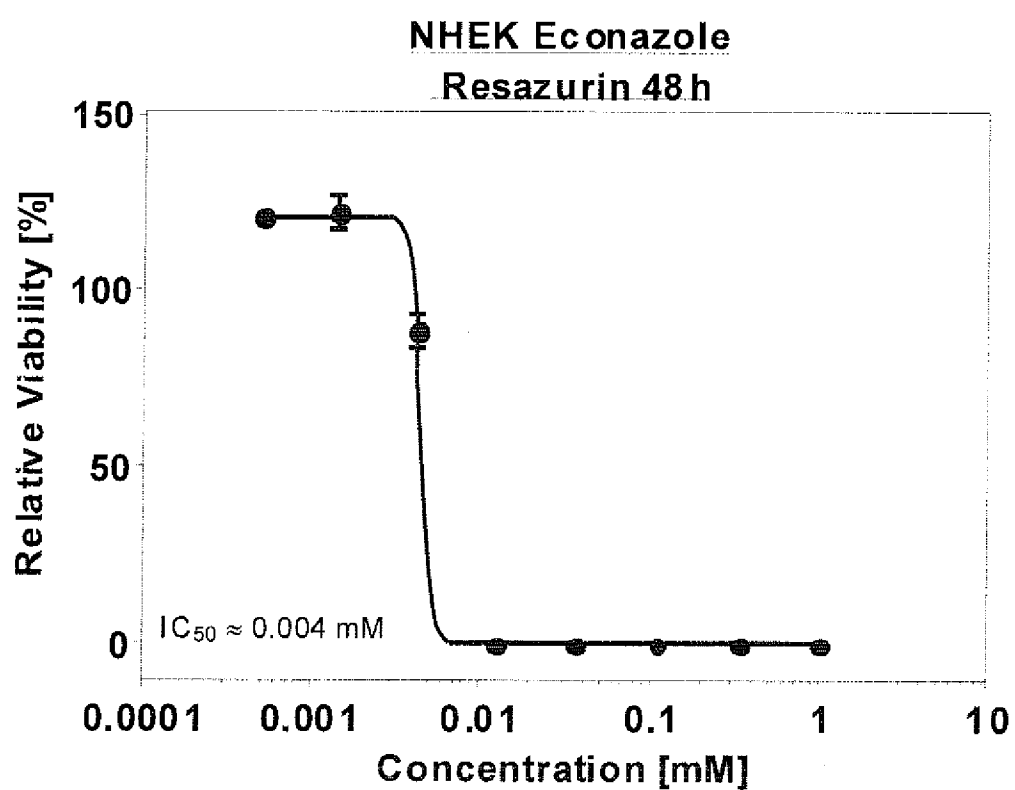


Fig. 5

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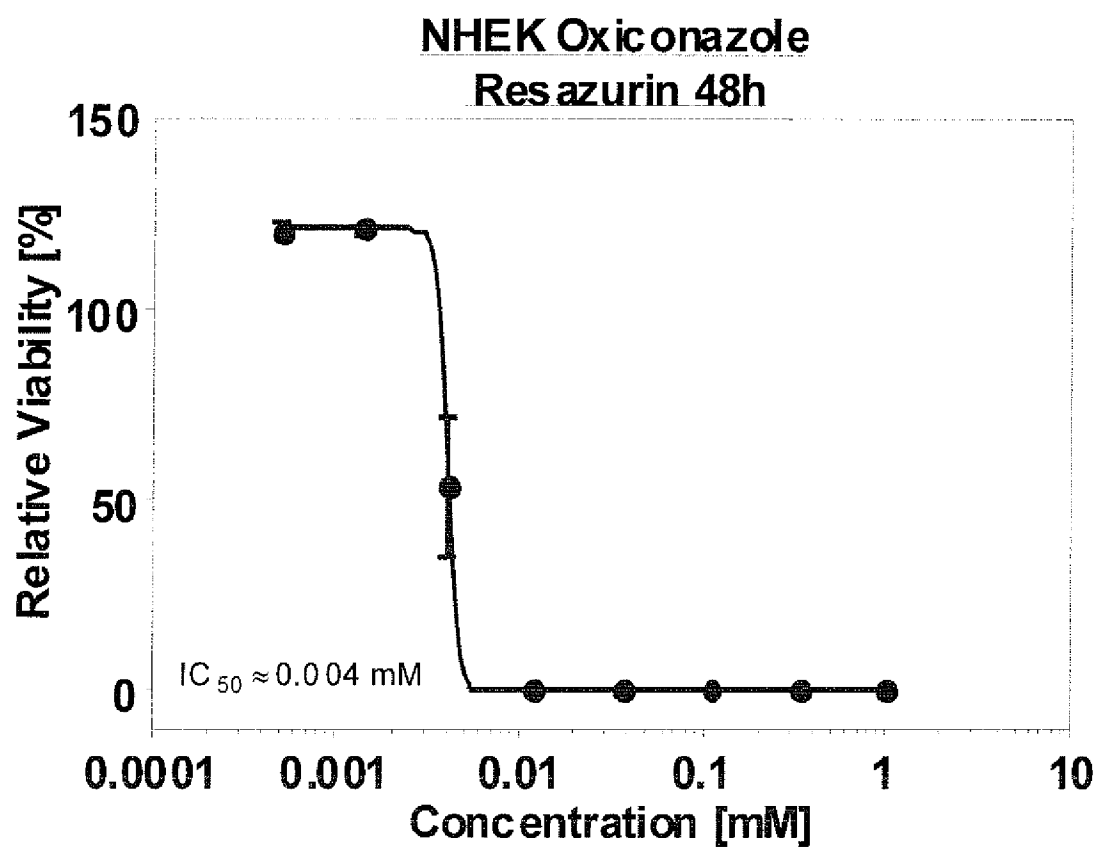


Fig. 6

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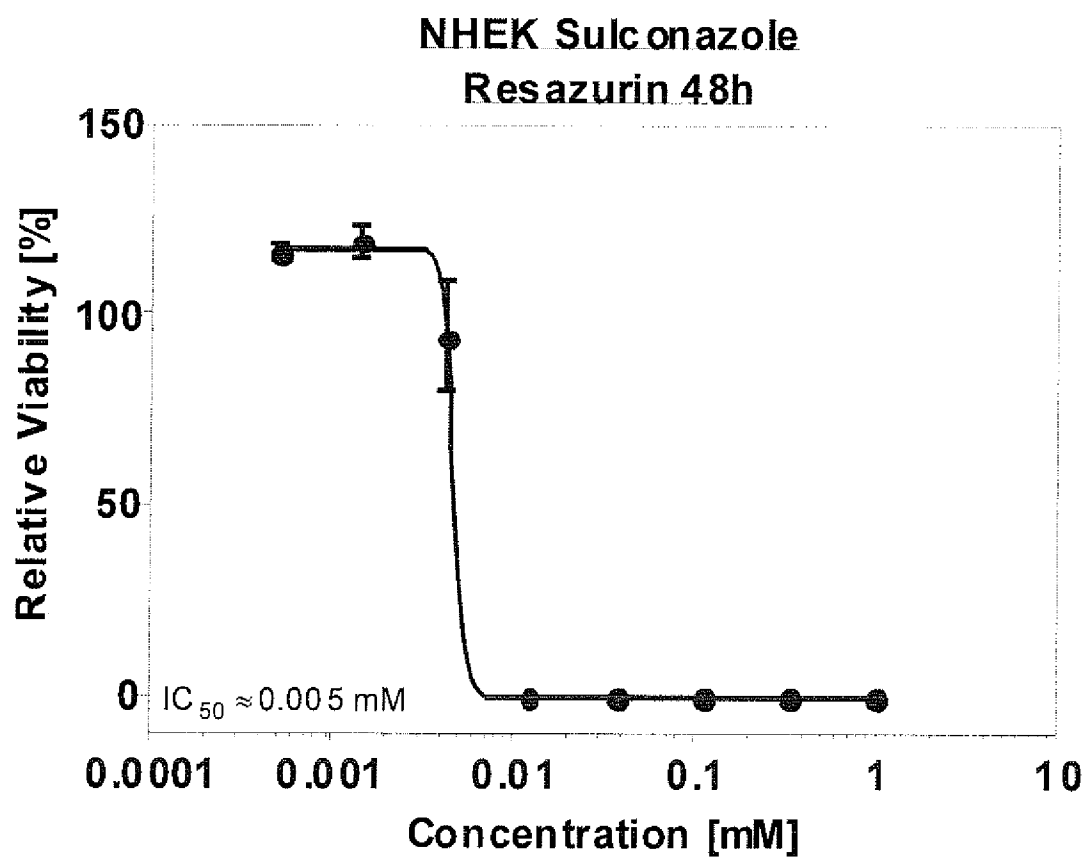


Fig. 7

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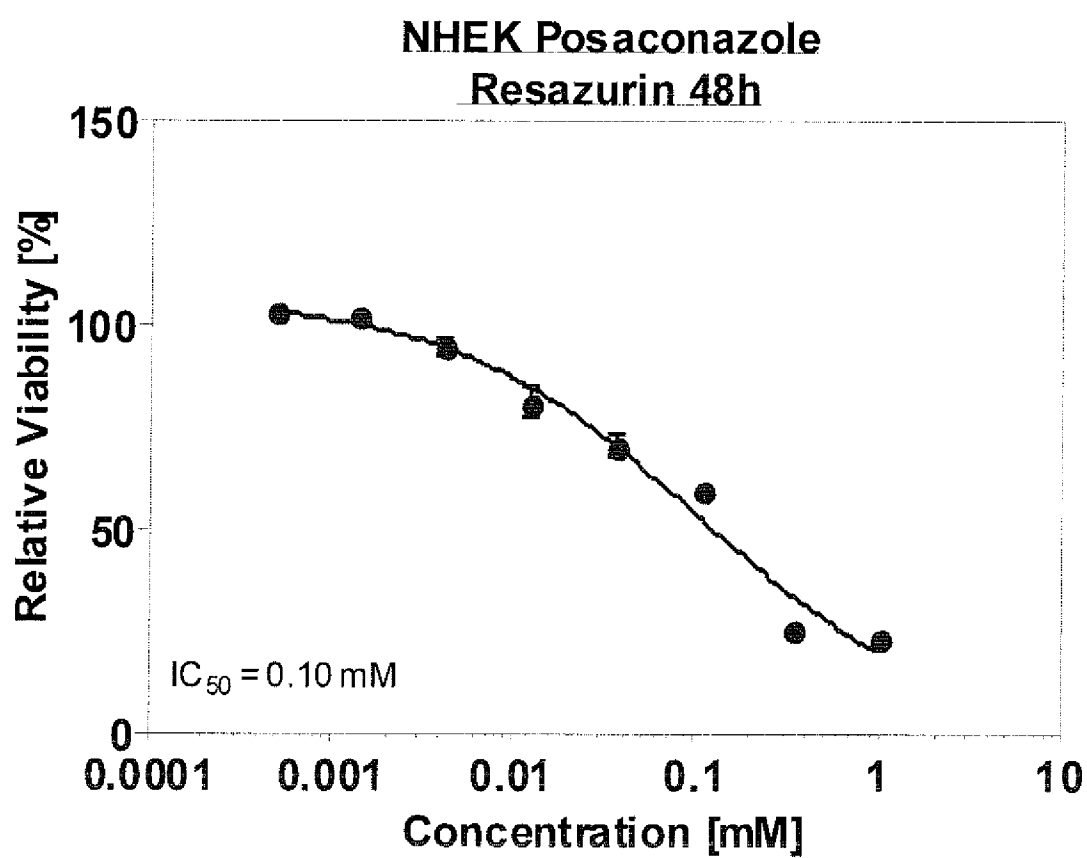


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/050819

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/41 A61K31/4174 A61K31/4178 A61K31/496 A61P17/00
A61P17/12 A61P17/16

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 556 871 A (HALPERIN JOSE [US] ET AL) 17 September 1996 (1996-09-17) column 2, lines 51-62 column 5, lines 34-48 column 6, lines 19-26 example 2 claims	1-8
X	EP 0 396 184 A2 (JANSSEN PHARMACEUTICA NV [BE]) 7 November 1990 (1990-11-07) page 3, lines 4-12 page 3, line 52 - page 4, line 14 page 4, lines 56-58 claims; examples	1-5,7,8
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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

8 February 2013

Date of mailing of the international search report

18/02/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Gradassi, Giulia

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/050819

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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International application No

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