Synthesis, Molecular Docking Studies and Antifungal Activity Evaluation of New Thiazolyl-methylene-1,3,4-oxadiazolines as Potential Lanosterol 14α-demethylase Inhibitors

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Considering the well-established antifungal activity ofazole compounds, a new series of thiazolyl-methylene-1,3,4-oxadiazolines derivatives were designed and synthesized as lanosterol-demethylase inhibitors. The final compounds were screened for antifungal activity against the Candida albicans ATCC 90028 strain. Molecular docking studies were performed to investigate the interaction modes between the compounds and the active site of lanosterol 14α-demethylase, which is a target enzyme for antifungal azoles. Theoretical ADME predictions were also calculated for the final compounds 5a-h.

Keywords: Thiazolyl-methylene-1,3,4-oxadiazolines, Candida albicans, lanosterol 14α-demethylase

Candida species represent the most common fungal pathogens that affect humans and the mortality associated with invasive mycosis increased in the last decade. Candida albicans is among the most diagnosed fungal species in clinical samples. This fungal strain lives as a commensal in the microbiome of healthy individuals, but can propagate as a pathogen in immunocompromised patients [1]. The azoles are the most widely used class of antifungal drugs. These compounds affect the integrity of fungal membranes, altering their morphology and inhibiting growth. This is achieved by inhibiting ergosterol biosynthesis via the inhibition of cytochrome P450's enzyme 14-α demethylase, which catalyzes the conversion of lanosterol to ergosterol. However, since this enzyme is similar to one found in the human liver, drug interactions due to metabolism can occur [2,3].

Prolonged use of azoles as antifungal agents has resulted in the emergence of drug resistance among certain fungal strains [4]. A novel strategy of generating a new class ofazole based antifungal agents is the merger of two or more biologically importantazole scaffolds, to achieve a target compound with improved activity [5-7]. To this end we chose two biologically importantazole scaffolds: thiazole and 1,3,4-oxadiazole and fused them together into one hybrid molecule taking account that compounds comprising each of these type ofazoles are associated with a broad spectrum of biological properties, including antifungal activity [8-14].

Following our research of novel azole based antimicrobial agents [15-17], we propose here the synthesis of some novel thiazolyl-methylene-1,3,4-oxadiazolines derivatives as possible antifungal agents. To investigate the interaction modes between the compounds and active site of lanosterol 14-5α-demethylase, a molecular docking study was performed.

Experimental part

Chemistry

Melting points were determined using open capillary tube method and are uncorrected. The purity of the synthesized compounds was verified by thin layer chromatography (TLC) and was carried out on pre-coated Silica Gel 60F254 sheets using heptan–ethyl-acetate 7:3 as developpant and UV absorption for visualization.

The 1H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the synthesized powder of the compounds in DMSO d6 (δH= 2.51ppm) as solvent and the spectra were recorded using a single excitation pulse of 12μs. GC-MS analyses were performed with an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond SE 52 capillary column. Elemental analysis was registered with a Vario El CHNS instrument.

All new compounds yielded spectral data consistent with the proposed structure and microanalysis within 0.4% of the theoretical values.

Synthesis of ethyl 2-(aryl)-thiazole-4-yl-acetate (2a-b) - general procedure

Compounds 2a-b were synthesized by refluxing a mixture of benzothioamide or 4-methyl-benzothioamide (30 mmol) with ethyl 4-bromo-3-oxobutanoate (30 mmol) in absolute ethanol (30 mL) for 1 h. After cooling, the mixture was poured in cold water and the oily liquid formed was separated by ether extraction and filtration over anhydrous sodium sulfate.

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2a: (E)-2-(2-phenyl-1,3-thiazol-4-yl)acetophenone: C17H14NO2S; Yield 90%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2). 2.40 (s, 3H, CH3).

2b: (E)-2-(2-(2-methoxyphenyl)-1,3-thiazol-4-yl)acetophenone: C17H15NO2S; Yield 90%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2). 2.40 (s, 3H, CH3).

3a-b: general procedure: 20 mmol of compound 2a or 2b and 1 mL of hydrazine hydrate were refluxed for 2 h in absolute ethanol (10 mL). The reaction mixture was cooled and the crystalline mass obtained was recrystallised from ethanol.

3a: (E)-2-(2-phenyl-1,3-thiazol-4-yl)acetophenone: C17H14NO2S; Yield 70%. m.p. 128-130°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

3b: (E)-2-[2-(2-p-tolyl)-1,3-thiazol-4-yl]acetophenone: C18H16NO2S; Yield 73%. m.p. 133-135°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

Synthesis of 2-arylthiazol-4-yl-acetohydrazides 3a-b - general procedure: equimolar quantities of 2-arylthiazol-4-yl-acetophenones 3a-b and various aromatic or heteroaromatic aldehydes were refluxed in absolute ethanol for 2 h. The solid product, formed after cooling, was filtered and dried. The crude solid was re-crystallised from ethanol.

4a: N’-[4-Cl-benzylidene]-2-(2-phenylthiazol-4-yl)acetohydrazide: C18H16NO2S; Yield 75%. m.p. 130-132°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4b: N’-[4-bromobenzylidene]-2-(2-phenylthiazol-4-yl)acetohydrazide: C18H16NO2S; Yield 85%. m.p. 161-164°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4c: N’-[4-nitrobenzylidene]-2-(2-phenylthiazol-4-yl)acetohydrazide: C19H18N2O2S; Yield 70%. m.p. 202-204°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4d: 1-(2-(2-phenylthiazol-4-yl)-N-((2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone: C22H19NO3S; Yield 80%. Yield 95%. m.p. 175-178°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4e: N’-[2-chlorobenzylidene]-2-(2-(2-p-tolyl)-1,3-thiazol-4-yl)acetophenone: C17H15NO2S; Yield 90%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4f: N’-[2-fluorobenzylidene]-2-(2-(2-p-tolyl)-1,3-thiazol-4-yl)acetophenone: C17H15NO2S; Yield 90%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

4g: N’-[2-methoxybenzylidene]-2-(2-(2-p-tolyl)-1,3-thiazol-4-yl)acetophenone: C17H15NO2S; Yield 90%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

5a: 1-(2-(4-chlorophenyl)-5-((2-(2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone: C19H16ClNO3S; Yield 85%. m.p. 175-178°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

5b: 1-(2-(4-methoxycarbonylphenyl)-5-((2-(2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone: C21H18ClNO3S; Yield 85%. m.p. 160-165°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

5c: 1-(2-(4-nitrophenyl)-5-((2-(2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone: C19H15NO4S; Yield 85%. m.p. 160-165°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).

5d: 1-(2-(2-phenylthiazol-4-yl)-5-((2-(2-phenylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone: C20H17NO2S; Yield 70%. m.p. 135-138°C. 1H NMR (DMSO-d6, δ, ppm): δ: 7.47-8.00, 5H phenyl, 7.22 (s, 1H, thiazole-5), 4.04 (s, 2H, CH2), 3.39 (s, 2H, CH2), 2.40 (s, 3H, CH3).
5h: 1-(2-(2,4-dichlorophenyl)-5-((2-(p-tolyl)thiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone C21H17Cl2N3O2S; Yield 75%. m.p. 160-165°C, MS (EI, 70eV): m/z 447 (M+2), 1H NMR (DMSO-d6, δ, ppm): 7.26-7.87, 6H (4H, tolyl, 3H o,p-diCl-phenyl, 1H, oxadiazol C2), 7.06 (s 1H, thiazole-5), 4.00 (s, 2H, CH2), 3.83 (s 3H, OCH3), 2.34 (s, 3H, tolyl-CH3), 2.23 (s, 3H, N-COCH3).

Anti-Candida Activity

The synthesized compounds 5a-h were screened against the Candida albicans ATCC 90028 fungal strain, by an adapted agar disk diffusion technique using a fungal suspension of 0.5 McFarland density obtained from 24 h cultures. The compounds were solubilized in dimethylsulfoxide to a final concentration of 1 mg/mL. A volume of 5µL of each tested compound’s solution was distributed directly on the solid medium previously seeded with the fungal inocula. The inoculated plates were incubated for 24 h at 37°C. Standard antifungal drug, ketoconazole, was also tested under similar conditions.

ADME study

In order to investigate the potential pharmacokinetic properties of the novel synthesized compounds, an ADME study was performed using Swiss-ADME (www.swissadme.ch).

Molecular docking study

A comparative molecular docking study was performed using AutoDock Vina [18] against fungal lanosterol 14α-demethylase (PDB: 5V5Z - Candida albicans), respectively against the human one (PDB: 3LD6 - Homo sapiens). Crystal structures of the enzymes were obtained from Protein Data Bank.

Dataset of compounds and the target structures were prepared using the previous reported protocol [19,20]. The grid boxes for both targets were configured as cube with sides x=y=z=28. Center coordinates of the search space for fungal enzyme were set to x=-38.49, y=-17.585, z=25.505 and for the human one to x=40.759, y=2.342, z=0.724. Molecular weight, partition coefficient (logP) and topological polar surface area (TPSA) were computed using FAF3-Drug [21].

Results and discussions

Chemistry

The final compounds (5a-h) were obtained by a four-step (Figure 1), convenient synthetic route. The 2-aryl-1,3-thiazole scaffold was easily achieved by a Hantzsch cyclization between appropriate thioamides 1a-b and ethyl 4-bromo-3-oxo-butanoate. Applying the hydrazinolysis of the esters 2a-b with hydrazine hydrate in absolute ethanol, the 2-(2-arylthiazol-4-yl)acetohydrazides 3a-b were prepared in satisfactory yields. These acetohydrazides, upon condensation with aromatic or heteroaromatic aldehydes, in absolute ethanol, afforded the corresponding hydrazones 4a-h. The obtained hydrazones were cyclised into the 1-(2-(aryl)-5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazol-3(2H)-yl)ethanones 5a-h (thiazolyl-methylene-1,3,4-oxadiazolines derivatives), by refluxing them with acetic anhydride (fig 1).

The structures of the newly synthesized compounds were elucidated by the combined use of 1H-NMR, mass spectral data and elemental analysis. The 1H-NMR spectra of compounds 4a-h showed a singlet signal at δ 8.48 - 8.63 ppm range corresponding to CH of the benzylidene group and another singlet signal at δ 10.75 - 11.58 ppm range due to the NH proton, hence confirming the formation of hydrazones. The 1H-NMR spectra of compounds 5a-h revealed the disappearance of azomethine and hydrazide protons and the occurrence of some new singlet signals at 7.2 - 7.6 ppm (1H) indicating CH resonance of the oxadiazoline ring and at 2.16 - 2.3 ppm (3H), which were attributed to the acetyl group protons (N-COCH3- in the 4 position of the oxadiazoline ring). MS findings were in accordance with the theoretical molecular formula of the compounds.

Antifungal Activity

Determination of Inhibition Zone Diameters

The synthesized compounds 5a-h were screened against the fungal strain of Candida albicans ATCC 90028. The obtained results are presented in Table 1, compared

Visualization and analysis of the docking results were performed using UCSF Chimera [22].

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>29</td>
</tr>
<tr>
<td>5b</td>
<td>24</td>
</tr>
<tr>
<td>5c</td>
<td>22</td>
</tr>
<tr>
<td>5d</td>
<td>20</td>
</tr>
<tr>
<td>5e</td>
<td>22</td>
</tr>
<tr>
<td>5f</td>
<td>24</td>
</tr>
<tr>
<td>5g</td>
<td>18</td>
</tr>
<tr>
<td>5h</td>
<td>22</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>24</td>
</tr>
</tbody>
</table>

Fig. 1. Chemical synthesis of the target compounds 5a-h.
with ketoconazole. The solvent used to prepare the solutions of the synthesized compounds, dimethylsulfoxide (DMSO), exhibited no inhibitory activity on the fungal strain used in the study.

Analyzing the results, we can observe that most of the tested compounds showed inhibition zone diameters inferior to or equal to ketoconazole, except the compound 5a that had an inhibition zone diameter superior to ketoconazole used as a standard drug. Concerning the relationships between the structure of the compounds and the anti-Candida activity, we observed that the compounds substituted with halogens (Cl, Br, F) in the para position of the oxadiazoline C-2-phenyl ring showed the biggest inhibition zone diameters (24-29 mm). Other type of substituents such as methoxy, nitro or halogens in ortho position seems to be less favorable for the antifungal action.

Theoretical Calculation of ADME Parameters

A computational study for the prediction of the ADME properties of the compounds 5a-h was performed, and the results are shown in Table 2. Topological polar surface area (TPSA) and log P are descriptors that are known to correlate well with passive molecular transport through membranes and thus have influence on metabolism, cell penetration, and bioavailability.

According to the Lipinski's rule of 5 [23], poor absorption or permeation is more likely when the molecular weight (MW) is greater than 500, the calculated log P is greater than 5 and TPSA values are 140 or more. Our results indicated that the majority of compounds (exception compound 5h - log P greater than 5) have good pharmacokinetic properties.

Molecular docking study

In order to provide an explanation for the mechanism of action of the synthesized compounds against C. albicans strain, docking studies were performed using AutoDock Vina software.

With the aim to evaluate and compare the binding affinity of our compounds to the fungal and the human lanosterol 14α-demethylase, the synthesized compounds 5a-h and ketoconazole, as a control inhibitor, were docked into the active site of both fungal and human lanosterol 14α-demethylase. The predicted affinity of compounds to the active site of both enzymes and the consequent inhibition constant (ki) are presented in Table 3. Inhibition constant (ki) was calculated based on the computed binding affinity energy (ΔG) using the formula: 

\[ \Delta G = R \cdot \ln(\frac{k_i}{K}) \]

\[ K = 10^{\frac{\Delta G}{R}} \]

where \( R \) is the gas constant (8.314 J mol\(^{-1}\) K\(^{-1}\)), \( T \) is the temperature (298.15 K), and \( K_i \) represents the association constant.

We have also calculated the fungal/human inhibition ratio (Table 3) in order to identify the compounds that inhibit selectively fungal lanosterol 14α-demethylase enzyme.

Analyzing the results of the docking study we identified three compounds (5a, 5b and 5f) that have better fungal/human inhibition ratio than ketoconazole meaning a superior selectivity for the fungal enzyme. We then focused on these compounds, while eliminating the others due to the lack of selectivity towards the fungal enzyme. The eliminated compounds had a less significant antifungal activity as determined by the diameters of the inhibition zone (Table 1).

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular weight (MW)</th>
<th>log P coefficient</th>
<th>Topological polar surface area (TPSA)</th>
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<tbody>
<tr>
<td>5a</td>
<td>397.88</td>
<td>4.23</td>
<td>83.03</td>
</tr>
<tr>
<td>5b</td>
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<tr>
<td>5c</td>
<td>468.43</td>
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</tr>
<tr>
<td>5h</td>
<td>411.89</td>
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<td>395.45</td>
<td>4.07</td>
<td>83.03</td>
</tr>
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</tr>
<tr>
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<td>446.35</td>
<td>5.23</td>
<td>83.03</td>
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</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding affinity (kcal/mol)</th>
<th>Inhibition constant (nM)</th>
<th>Binding affinity (kcal/mol)</th>
<th>Inhibition constant (nM)</th>
<th>Fungal / human inhibition ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
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<td>3.14</td>
<td>-11.1</td>
<td>6.17</td>
<td>0.51</td>
</tr>
<tr>
<td>5b</td>
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</tr>
<tr>
<td>5c</td>
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<td>3.14</td>
<td>-11.5</td>
<td>3.72</td>
<td>0.84</td>
</tr>
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<td>5d</td>
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<td>10.24</td>
<td>-12.2</td>
<td>1.14</td>
<td>6.97</td>
</tr>
<tr>
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<td>3.14</td>
<td>-11.6</td>
<td>3.14</td>
<td>1.00</td>
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<tr>
<td>5f</td>
<td>-11.9</td>
<td>1.89</td>
<td>-11.7</td>
<td>2.65</td>
<td>0.71</td>
</tr>
<tr>
<td>5g</td>
<td>-11.2</td>
<td>6.17</td>
<td>-11.3</td>
<td>5.21</td>
<td>1.18</td>
</tr>
<tr>
<td>5h</td>
<td>-11.6</td>
<td>2.24</td>
<td>-11.7</td>
<td>2.65</td>
<td>0.84</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>-12.3</td>
<td>0.95</td>
<td>-12.26</td>
<td>1.04</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Molecular docking showed that our compounds did not covalently interact with the heme from the active site of lanosterol 14α-demethylase, like classic antifungal azoles (e.g. ketoconazole). However, they interact with the amino acids located in the access channel to the enzyme’s active site, such as: LEU376, HIS377, LEU87, VAL234, PHE 233 and PHE463. As a result, we can assume that the newly synthesized compounds act as non-competitive inhibitors of the enzyme. This supposition implies that a slightly different mechanism of action is in play (compared to classic antifungal azoles) which could...
promise a protection against fungal resistance mechanisms and also a reduced hepatic toxicity [8].

The synthesized compounds comprise two different substitutions as phenyl or tolyl on C-2 position of thiazole ring. Docking results showed that this modification in structure did not cause a significant change in the interaction manner. For a significant change a substituent larger than methyl should be introduced.

The presence of the halogen atoms in the para position of the terminal aromatic ring leads to a better molecular lipophilicity, with no significant changes in target interaction. Substitution with halogen atoms in other positions, such as meta or orto would result only in pharmacokinetic changes, because there are no amino acid residues in the proximity for potential interactions.

The oxadiazoline ring acts more like a hinge, than a pharmacophore. No polar interactions are made by atoms from this ring, the only vicinal amino acid residue being Leu376. However, the oxadiazoline ring carries the acetyl residue, important for polar contact with His377 in all molecules.

Conclusions

In the current work, a series of new thiazolyl-methylenoxadiazolines (5a–h) were synthesized and evaluated for their in vitro anti-Candida activities. Results of the antifungal study indicated that compound 5a has a significant antifungal activity, better than the standard ketoconazole. Furthermore, docking studies showed that these compounds interact with the amino acids from the access channel to the active site of the lanosterol 14α-demethylase and not with the heme moiety, as do classical antifungal azoles. As such, these compounds could have the advantage of a slightly different mechanism of action that would translate into a reduced risk for the emergence of antifungal resistance and an improved safety profile. ADME predictions also support the druggability of these compounds.

As a result it can be stated that the synthesized compounds should be further developed in order to identify new antifungal agents with higher potency and tolerably.

References


Manuscript received: 15.12.2018