Anticandidosic Activities of New Chalcones Vectorised By Benzimidazole against a Strain of Candida Albicans Pharmacoresistance to Azoles

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Abstract: The objective of this work was to determine the anticandidosic activities of new chalcones against a clinical strain of Candida albicans resistant to antifungal Azole, and then to determine the structural elements conducive to induction of anticandidosic activities. Ten chalcones hybrids, all of which contain phenylpropenone or pyridinylpropenone chains in their respective molecules, have been designed, synthesized and characterized. In order to select the active compounds at the 10 µg threshold, an antifungal screening was performed using the bioautographic method. The Minimum Inhibitory Concentrations (MICs) of the selected compounds were then determined in vitro on the clinical strain of Candida albicans using the microplate dilution method. Among the 10 compounds evaluated, 6 derivatives presented antifungal activity. The reference substances (Fluconazole and Ketoconazole) showed no activity during screening at the 10 µg threshold amount. In addition, the best anticandidosic performance was achieved with C5-halogenated derivatives with MICs of 1.25 µg / ml. Our pharmacochimical approach has led to the development of new molecules with benzimidazolyl-arylpropenone structure with anticandidosic activities. This innovative chemical profile opens up new and important avenues of investigation for the development of new antifungal agents.

Keywords: Benzimidazole. Arylpropenone. Chalcone. anticandidosic. Candida albicans.

Date of Submission: 25-07-2018
Date of acceptance: 12-08-2018

I. Introduction
Candidiasis infections have experienced a resurgence in recent years, with the increase in immunodeficiency situations [1-3]. This resurgence of candidiasis, especially in immunocompromised subjects, is a public health problem [4]. In addition, the drug management of candidiasis, which was once very effective with the use of Azoles antifungal agents, is currently confronted with strong drug resistance in some Candida strains [5-6]. In this context, it is necessary to develop new molecules that are not resistant to these drugs. This is why we have taken an interest in the benzimidazole heterocycle, which carries in its position 2 the functional arylpropenone chain of chalcones as a potential new anticandidosis. This interest in the benzimidazole nucleus is explained by the fact that it constitutes the heterocyclic support of Chlormidazole, the first synthetic antifungal agent[7-8]. In addition, benzimidazole is primarily a nitrogenous nucleus resulting from the binding of benzene and imidazole. This heterocycle could have anticandidiodit properties, such as antifungal azoles. As for the arylpropenone functional sequencing of chalcones, its ability to bind certain thiol-functional infectious enzymes (glutathione S-transferase, cysteine, keratin, etc.) would currently explain the use of its acceptors for the development of new anti-infectious drugs [9-11]. For all these reasons, our research team has conceptualized, synthesized and characterized chalcone hybrids for anti-infectious purposes. After evaluating the anthelmintic and antiplasmodic activities of the said chalcones [12-13], it seemed logical to evaluate their antifungal activities against a clinical strain of Candida albicans pharmacoresistant to Azoles. These benzimidazole supported chalcone hybrids could lead to drug candidates that are effective against Candida albicans. The objective of this work is to determine the Minimum Inhibitory Concentrations of these chalcones in relation to C. albicans strain and then to establish the structural elements favourable to the desired Anticandidosic activities.

DOI: 10.9790/3008-1304051116 www.iosrjournals.org 11 | Page
II. Experimental

1. Reagents, Instrumentation and Measurements

For all compounds, nuclear magnetic resonance spectra (1H, 300 MHz and 13C, 75 MHz) were recorded on a Bruker advance 300 instrument. Mass spectra (MS) were recorded on an HP 5889 quadrupole spectrometer using electronic impact (EI). TLC were carried out using Merck aluminum backed sheets coated with 60 F254 silica gel. The melting points (PF) were determined using a Kofler bench and are not corrected. Solvents and reagents come from Sigma Aldrich (France) or Acros Organics (France). Antifungal drugs (Ketoconazole and Fluconazole) in the form of pure powders come from Sigma Chemical Co (USA).

2. General procedure for compounds (3a-j)

Access to chalconic derivatives required the prior synthesis of a raw material, namely 2-acetylbenzimidazole, which may or may not be substituted in position 5. This raw material has been obtained by condensation according to the Phillips method [14] (Phillips M. 1928). Between various suitably selected orthophenylenediamines and lactic acid. All the different reaction stages of access to 2-acetylbenezimidazole have been described in a previous work [15]. Subsequently, the 2-acetylbenezimidazoles (1) prepared were engaged in a Claisen-Schmidt type basic condensation reaction with benzaldehyde or with its pyridine analogue (nicotinaldehyde) (2) to lead to the expected new chalcones (3a-3j) (Figure 1). The general method of access to chalcones consisted in adding to an ethanolic solution of sodium hydroxide (75 mmol of sodium hydroxide in 40 ml of ethanol) 2-acetylbenezimidazole (1.5 g, 10 mmol) and arylaldehyde (10, 1 mmol) corresponding. The reaction medium is stirred for 3 to 5 hours at ambient temperatures. After neutralization of the medium with a solution of 30% acetic acid, the precipitate formed was filtered, dried and then recrystallized in a suitably chosen solvent. By proceeding, in this way we isolated 10 chalcones (Table I) all possessing in their respective structures the phenylpropenone (3a, 3c, 3e, 3g, 3i) or pyridinylpropenone (3b, 3d, 3f, 3h, 3j) chain.

![Figure 1](https://example.com/figure1.png)

Figure 1: Synthesis of benzimidazolyl-chalcone.

(E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (3a)

Yield = 78%; Yellow solid; mp = 216 °C. 1H NMR (DMSO-d6, δ ppm): 14 (1H, s, N-H); 8,28 (1H, d, J = 16 Hz, CH=N); 8,15 (1H, d, J = 16 Hz, CH=CH); 8,02 (2H, m, Har); 7,90 (2H, m, Har); 7,2 (2H, m, Har); 7,09 (2H, m, Har); 7,06 (1H, m, Har). 13C NMR (DMSO-d6, δ ppm): 181,13 (C=O), 149,49 (C=N); 134,97 (CH=CH); 139,87 (Car); 134,75 (2Car); 128,77 (Car); 124,22 (2Car); 122,51 (2Car); 122,70 (2Car); 121,69 (CH=CH); 117,03 (2Car). ES+ SM: 249 [M+H]+.

(E)-1-(1H-benzimidazol-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one (3b)

Yield = 50%; Yellow solid; mp = 244 °C. 1H NMR (DMSO-d6, δ ppm): 13,60 (1Hs, N-H); 9,0 (1H, d, J = 2 Hz, Hα); 8,80 (1H, d, J = 2 Hz, Hβ); 8,65 (1H, m, Hα); 8,35 (1H, m, Hβ); 8,25 (1H, d, J = 16,2 Hz, CH=N); 8,05 (1H, d, J = 16,2 Hz, CH=CH); 7,60 (2H, m, Hα); 7,35 (2H, m, Hβ). 13C NMR (DMSO-d6, δ ppm): 182,13 (C=O); 154,02 (Car); 150,77 (Car); 150,09 (C=N); 144,27 (CH=CH); 139,87 (Car); 134,75 (2Car); 124,22 (2Car); 122,51 (2Car); 122,19 (CH=CH); 120,89 (Car); 117,03 (2Car). ES+ SM : 250 [M+H]+.

(E)-1-(5-benzoyl-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (3c)

Yield = 75%; Yellow solid; mp = 210 °C. 1H NMR (DMSO-d6, δ ppm): 14,0 (1H, s, N-H); 8,11 (1H, d, J = 18 Hz, Hα); 8,04 (1H, s, Hβ); 7,86 (1H, d, J = 18 Hz, Hβ); 7,73-7,79 (5H, m, Hα); 7,70 (1H, s, Hα); 7,64 (1H, d, Hα); 7,58 (2H, m, Hβ); 7,54 (2H, m, Hβ); 7,51 (1H, m, Hα). 13C NMR (DMSO-d6, δ ppm): 195,42 (C=O), 180,83 (C); 151,03 (C); 144,90 (C); 137,60 (C); 134,15 (C); 133,0 (C); 132,38 (C); 131,25 (C); 129,53 (C); 129,14 (C); 129,90 (C); 128,48 (C); 127,03 (C); 126,18 (C); 124,22 (C); 122,70 (C); 122,51 (C); 121,69 (C); 120,89 (C). ES+ SM: 353 [M+H+].
Anticandidosic Activities Of New Chalcones Vectorised By Benzimidazole Against A Strain

(E)-1-(5-benzoyl-1H-benzimidazol-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one (3d)
Yield = 55 %; Yellow solid; mp = 186 °C. 1H NMR (DMSO-d6, δ ppm): 14.0 (1H, s, N-H); 9.0 (1H, s, H3); 8.90 (1H, d, J = 2 Hz, H2); 8.35 (1H, m, H2); 8.02 (1H, s, H2); 7.97 (1H, d, J = 18 Hz, H1); 7.90 (1H, m, H3); 7.86 (1H, d, J = 18 Hz, H2); 7.73-7.59 (5H, m, H8 & H2); 7.70 (1H, s, H3); 7.64 (1H, d, H4). 13C NMR (DMSO-d6, δ ppm): 195.41 (C16), 180.75 (C1), 154.02 (C8), 151.12 (C10), 150.77 (C14), 144.95 (C5), 137.61 (C1), 135.41 (C13a), 133.0 (C10), 132.38 (C11), 131.41 (C13), 131.22 (C12), 129.53 (C18), 129.14 (C14 et C2), 129.0 (C19 et C2), 127.03 (C12), 126.18 (C14), 124.22 (C9), 122.51 (C15), 121.69 (C2), 120.89 (C3). ES+ SM: 354 [M+H+].

(E)-1-(5-chloro-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (3e)
Yield = 78 %; Yellow solid; mp = 228 °C. 1H NMR (DMSO-d6, δ ppm): 13.50 (1H, s, N-H); 8.10 (1H, d, J = 16 Hz, H2); 7.97 (1H, d, J = 16 Hz, H2); 7.85 (1H, m, H12); 7.76 (1H, m, H13); 7.46-7.51 (5H, m, H5, H6, H8, H9 et H10); 7.25 (1H, m, H4).

(E)-1-(5-chloro-1H-benzimidazol-2-yl)-3-pyridin-3-ylprop-2-en-1-one (3f)
Yield = 61 %; Yellow solid; mp = 188 °C. 1H NMR (DMSO-d6, δ ppm): 14.0 (1H, s, N-H); 9.07 (1H, d, H3); 8.96 (1H, d, H3); 8.50 (1H, m, H2); 8.35 (1H, m, H2); 8.00 (1H, d, H3); 8.03 (1H, d, J = 16 Hz, H2); 8.12 (1H, d, J = 16 Hz, H2); 7.85 (1H, s, H1); 7.70 (1H, m, H8).

(E)-1-(5-fluoro-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (3g)
Yield = 77 %; Yellow solid; mp = 219-221°C. 1H NMR (DMSO-d6, δ ppm): 13.50 (1H, s, N-H); 8.10 (1H, d, J = 16 Hz, H2); 7.96 (1H, d, J = 16 Hz, H2); 7.86 (1H, m, H12); 7.76 (1H, m, H13); 7.47-7.52 (4H, m, H5, H6, H8, et H9); 7.23 (1H, m, H14). 13C NMR (DMSO-d6, δ ppm): 181.92 (C16), 154.52 (C3), 151.07 (C12), 150.19 (C10), 145.01 (C13), 143.86 (C16), 141.76 (C15a), 139.20 (C4), 133.0 (C11a), 127.63 (C12), 122.59 (C14), 124.22 (C9), 121.69 (C2), 120.80 (C3), 117.53 (C5).

(E)-1-(5-fluoro-1H-benzimidazol-2-yl)-3-pyridin-3-ylprop-2-en-1-one (3h)
Yield = 55 %; Yellow solid; mp = 189 °C. 1H NMR (DMSO-d6, δ ppm): 14.0 (1H, s, N-H); 9.07 (1H, d, H3); 8.96 (1H, d, H3); 8.50 (1H, m, H2); 8.35 (1H, m, H2); 8.30 (1H, d, J = 16 Hz, H2); 8.12 (1H, d, J = 16 Hz, H2); 7.86 (1H, m, H12); 7.70 (1H, m, H13); 7.25 (1H, m, H8). 13C NMR (DMSO-d6, δ ppm): 181.0 (C16), 154.52 (C3), 151.40 (C10), 150.19 (C12), 145.01 (C13), 143.86 (C16), 141.76 (C15a), 139.20 (C4), 133.0 (C11a), 125.70 (C12), 124.22 (C9), 121.69 (C2), 120.80 (C3), 119.90 (C14), 117.03 (C5). ES+ SM: 267 [M+H+].

(E)-1-(5-nitro-1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (3i)
Yield = 72 %; Yellow solid; mp = 258 °C. 1H NMR (DMSO-d6, δ ppm): 14.0 (1H, s, N-H); 8.54 (2H, m, H12); 8.28 (1H, d, J = 16 Hz, H2); 8.28 (1H, d, J = 16 Hz, H2); 8.20 (1H, m, H13); 8.12 (1H, d, J = 16 Hz, H2); 7.90 (1H, m, H12); 7.20 (2H, m, H2 et H3); 7.09 (2H, m, H8 et H9); 7.06 (1H, m, H4). 13C NMR (DMSO-d6, δ ppm): 181.19 (C16), 153.72 (C3), 144.89 (C1), 143.97 (C3), 143.82 (C15a), 142.55 (C11a), 139.90 (C4), 131.23 (C12), 128.77 (C1), 124.22 (C9), 122.51 (C14), 122.70 (C6 et C8), 121.69 (C2), 120.89 (C3), 117.03 (C5). ES+ SM: 294 [M+H+].

(E)-1-(5-nitro-1H-benzimidazol-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one (3j)
Yield = 57 %; Yellow solid; mp = 242 °C. 1H NMR (DMSO-d6, δ ppm): 13.60 (1H, s, N-H); 9.07 (1H, d, J = 2 Hz, H2); 8.96 (1H, d, J = 2 Hz, H2); 8.50 (1H, m, H12); 8.35 (1H, m, H2); 8.25 (1H, d, J = 16 Hz, H1); 8.05 (1H, d, J = 16 Hz, H2); 8.02 (1H, s, H2); 7.70 (1H, s, H3); 7.64 (1H, d, H4). 13C NMR (DMSO-d6, δ ppm): 182.0 (C16), 154.02 (C15), 150.77 (C7), 150.09 (C10), 145.31 (C13), 144.27 (C9), 139.87 (C7), 135.41 (C15a), 133.0 (C11a), 127.03 (C12), 124.22 (C9), 122.58 (C14), 121.69 (C2), 120.89 (C3), 117.53 (C5). ES+ SM: 295 [M+H+].

3. Anticandididic assays

Candida albicans strain

The clinical strain of Candida albicans "27506 CeDReS strain", was provided by the Center for Diagnosis and Research on AIDS and Opportunistic Diseases (CeDReS) of the University Hospital of Treichville Abidjan (Ivory Coast). An antifungigram using the agar diffusion method was previously performed to determine the susceptibility of these strains to antifungal azoles (Ketoconazole, Fluconazole). Results from the antifungigram show resistance to Ketoconazole and Fluconazole (Table I).

DOI: 10.9790/3008-1304051116  www.iorsjournals.org  13 | Page
Table I: Antifungigram of the clinical strain of Candida albicans "27506 CeDReS" against two antifungal azoles

<table>
<thead>
<tr>
<th>Antifungal azoles</th>
<th>Clinical strain of Candida albicans “strain 27506 CeDReS”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Resistant</td>
</tr>
<tr>
<td>Flavocazole</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Antifungal screening by bioautography technique

Products in powder form were first solubilized in methanol for the preparation of stock solutions titrating to 1 mg/ml. From each of these stock solutions, a range of 10 dilutions of reason 2 was prepared. Then, 10 μl of each solution were deposited on glass plates in Silicagel 60 F254. The chromatograms were previously developed in saturated tanks of a mobile chloroform-methanol-water phase in a ratio (65:35:5) and then dried. In addition, Candida albicans fungal inoculum containing approximately 105 cells/ml was obtained by seeding three colonies of a pure strain for 24 to 48 hours in Tryptone Soya broth. This inoculum was spread on each chromatogram. The plates were incubated at 30°C after solidification of the agar for 24 hours. The plates, then obtained, were impregnated with an aqueous solution of methylthiazolyl chloride Tetrazolium and incubated for 2 to 4 hours. Areas of growth inhibition subsequently appear as white spots on a purple background [16]. Only those products that have shown a inhibitory zone at the 10 μg threshold amount have been selected for the determination of Minimum Inhibitory Concentrations (MICs).

Determination of Minimum Inhibitory Concentrations (MIC) by microplate dilution technique

The evaluation of antifungal efficacy by determining the Minimum Inhibitory Concentrations (MICs) was made using the microplate dilution technique. This technique consists of contacting a Candida inoculum with an increasing dilution of selected products in 96 well microplates. The preparation of the fungal inoculum is done as previously described in the bioautography technique. The stock solutions of benzimidazolylarylpropenones were prepared with Dimethylsulfoxide (DMSO) at a concentration of 1 mg/ml and then diluted with broth to obtain concentrated solutions at 100 μg/ml. Subsequently, 100 μl of this dilution was deposited in the wells in the first column and 50 μl of broth was distributed to the following wells. Subsequently, 50 μl were taken from the first 100 μl of the first well to achieve a range of dilutions increasing for reason 2. Finally, 50 μl of inoculum was distributed to the wells except for the last one, which serves as a control to verify that there is no contamination. The plates were incubated at 30°C for 48 hours. For the revelation of the prepared microplates, 40 μl of aqueous solution of Methyl Thiazolyl Chloride Tetrazolium (MTT) at a concentration of 2.5 mg/ml was distributed to the wells and incubated for a further 30 minutes at room temperature. Wells containing still active cells turn yellow to violet as a result of mitochondrial dehydrogenase activity. The MIC is given by the lowest concentration at which MTT does not turn purple.

III. Results and Discussion

The results of the antifungal screening showed that of the ten derivatives evaluated, only six derivatives exhibited antifungal activity at the threshold quantity of 10 μg (Table II). In fact, the Minimum Inhibitory Concentrations (MIC) determined by microplate dilutions showed that, in series, phenylpropenone derivatives, only the compounds (3a, 3e, 3g) were active on the Candida strain with concentrations ranging from 5 to 1,25μg / ml. On the other hand in series of pyridinylpropenone derivatives, it is the compounds (3d, 3f, 3h) that have been active on the Candida strain for concentrations of between 5 and 1.25 μg / ml. In addition, the reference drugs (Fluconazole and Ketoconazole) proved to be inactive on the C. albicans strain at the limit of our experiment (QMI = 10 μg).

Table II: In vitro antifungal activities of 3a-3j compounds and reference substances with respect to Candida albicans.

<table>
<thead>
<tr>
<th>General structure</th>
<th>Compounds</th>
<th>R</th>
<th>X</th>
<th>Candida albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3a</td>
<td>H</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>N</td>
<td>-</td>
<td>Nd</td>
</tr>
<tr>
<td></td>
<td>3c</td>
<td>CH</td>
<td>-</td>
<td>Nd</td>
</tr>
<tr>
<td></td>
<td>3d</td>
<td>N</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3e</td>
<td>Cl</td>
<td>+</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>3f</td>
<td>N</td>
<td>+</td>
<td>1.25</td>
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<tr>
<td></td>
<td>3g</td>
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</tr>
<tr>
<td></td>
<td>3h</td>
<td>N</td>
<td>+</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>3i</td>
<td>CH</td>
<td>-</td>
<td>Nd</td>
</tr>
<tr>
<td></td>
<td>3j</td>
<td>N</td>
<td>-</td>
<td>Nd</td>
</tr>
</tbody>
</table>
Anticandidosic Activities Of New Chalcones Vectorised By Benzimidazole Against A Strain

<table>
<thead>
<tr>
<th>Kétokonazole</th>
<th>-</th>
<th>Nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>Nd</td>
</tr>
</tbody>
</table>

(+): Active (QMI = 10µg)
(-): Inactive (QMI > 10µg)

nd: not determined as inactive for antifungal screening at the 10 µg threshold quantity.

Results of the antifungal screening and antifungigram revealed that Candida strain showed decreased susceptibility to antifungal azoles (Fluconazole and Kétokonazole). This clinical strain of Candida being isolated in AIDS patients, the resistance observed could be explained by the systematic use of antifungal Azoles in prophylactic or curative treatment of fungal infections in his patients. Indeed, cases of resistance have been reported in people living with HIV/AIDS who have received long-term treatment with Fluconazole [17-18]. Thus, the current medical consensus, which advocates the prevention of candidiasis prophylaxis in immunocompromised subjects, would favour the selection of resistant isolates and cross-resistance to antifungal Azoles [19-20]. A structure-activity relationship analysis of said results shows that the adhesion of benzimidazole to phenylpropenone chain reaction in Compound 3a induced anti-Candida albicans activity with an MIF of 5 µg / ml. Such efficacy on the Azolee-resistant clinical strain corroborates the intrinsic anti-infectious potential of the phenylpropenone functional grouping of chalcones and the benzimidazole heterocycle [21-23]. The replacement of the benzene nucleus of phenylpropenone of Compound 3a with its pyridine-type nitrogen isoster led to pyridinylpropenone in Compound 3b. However, such chemical modulation has led to annihilation of the antican didiac activities. This result shows that the concept of ring isothermia alone is not sufficient to induce an anticandidotic serial activity of pyridinylpropenone. Thus, to induce the biological activities of Compound 3b, we have introduced various modulators (benzoyl, halogen and nitro) in position 5 of benzimidazole, such as benzimidazole anthelmintics [24]. For example, the introduction of a benzimidazole benzyl group in position 5 of benzimidazole led to activity against the serial Candida albicans strain of pyridinylpropenones at the MIC of 5 µg/ml (Compound 3d). On the other hand, the C5-benzoyl derivative (Compound 3c) did not exhibit any activity at the 10 µg threshold amount during antifungal screening as a series of phenylpropenone derivatives. Thus, the presence of the benzyl group led to an inversion of the anticandidotic efficacy. Furthermore, the presence of a halogen atom (chlorine or fluorine) in the C5 position of benzimidazole has led to the maintenance or even improvement of antican didiac activities. Indeed, with a MIC of 1.25 µg/ml, the 5-chlorinated phenylpropenone derivative (Compound 3) showed a similar efficacy to the 5-chlorinated pyridinylpropenone derivative (Compound 3f). Such an anti-Candida performance is 4 times higher than that of Compound 3a on the same strain (MIC = 5 µg/ml). Replacing the chlorine atom with another fluorine-type halogen led to the 5-fluorinated phenylpropenone derivative (compound 3g) with a 5 µg/ml and the 5-fluorinated pyridinylpropenone derivative (compound 3h) with a MIC of 2.5 µg/ml. These fluorinated derivatives have proven to be less effective than chlorinated derivatives but this activity remains higher than that of Compound 2a. In the end, chlorinated and fluorinated derivatives showed the best anticandididosic performances compared to the C. albicans strain. Such a performance of halogenated derivatives would undoubtedly be due to their greater lipophilicity. Indeed, this additional degree of lipophilia may be necessary to cross the lipidic fungal membrane and interact with a possible biological target such as ergosterol. C5-nitration, on the other hand, led to a loss of antifungal activity of C5-nitrate derivatives (composed of 3i and 3j) at the threshold quantity 10 µg, whatever the series considered. Thus, unlike other drug series (5-nitro imidazolated, 5-nitro furans) where the presence of the nitro group in position 5 is essential to induce anti-infectious properties, it is not very conducive to induction of antifungal activities in the benzimidazolyl-arylpropenone series.

IV. Conclusion

The purpose of this pharmacochemical work was to evaluate the antifungal activities of new benzimidazolyl-chalcones against a clinical strain of pharmacochemo-chemosensitive Candida albicans. This study showed that these chalcones are molecules with high antifungal potential with MICs between 5 and 1.25 µg/ml. The structure-activity relationship type discussion established that in the benzimidazolyl-phenylpropenone series, the best performance on this clinical strain is obtained with C5-chlorinated derivatives with MICs of 1.25 µg/ml. In addition, as a series of benzimidazolyl-pyridinylpropenones, the induction of antifungal activities is subject to the introduction of a halogen atom or a C5 benzoyl group of the benzimidazole ring. These notable antifungal activities in relation to this strain of Candida albicans resistant to Azoles, open up significant avenues of investigation for the development of new antifungal agents capable in series production of arylpropenones with benzimidazolic support.

Acknowledgement

The authors express their deep gratitude to the Swiss Center for Scientific Research in Côte d'Ivoire (for anticandidosic tests); CEISAM, Laboratory of the University of Nantes (for chemical reagents, MS and NMR spectroscopy) and OELA Group Côte d'Ivoire (for chemical reagents).
**Bibliographic References**


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