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Synthesis and Anticandidosic Activities of Some 3-Imidazo[1,2-a]Pyridinyl-1-Arylpropenone Derivatives

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Abstract

In this work, we show the synthesis of ten (10) new derivatives of 3-imidazo [1,2-a]pyridinyl-1-arylpropenone (10a - d). These new compounds were obtained by condensation of Claisen-Schmidt between derivatives of 2-substituted-1*H*-imidazo[1,2-a]pyridine-3-carbaldehyde (3a - b and **7**) and acetophenone derivatives (9a - e) in the presence of a base. The synthesized compounds were characterized by spectroscopic analyses ^{1}H and ^{13}C NMR. The antifungal activity of the ten (10) derivatives was determined on a resistant strain of *Candida albicans* by the microdilution method. The results showed that four (4) of them (10a, 10b, 10c and 10i) were active with minimum inhibitory concentrations (MICs) below 300 µmol/L. Of these four compounds, 10i was more potent than the others with a MIC of 41.98 µmol/L.

Keywords

Imidazo[1,2-a]Pyridine, Arylpropenone, *Candida albicans*, Antifungal

1. Introduction

Candida albicans (*C. albicans*) is a commensal fungus of humans and mammals [1] [2]. Usually harmless, it could become pathogenic and responsible of various types of infections, among which we may place candidiasis [3] [4] [5]. These are mostly superficial but significantly more common in immunocompromised pa-

tients (cancer, diabetes, HIV-AIDS, etc…) [6] [7] [8]. This type of population is especially susceptible to development of deep candidiasis: meningitis, or even sepsis. These infections are severe with a life-threatening prognosis. Efficient therapies and effective treatments (azoles and echinocandins) improve the prognosis of patients [9]. However, the emergence of strains resistant on these antifungals specifically, makes patient management more restrictive [10] [11]. It is therefore useful to develop new antifungals capable of circumventing these resistance mechanisms while ensuring the security of the administration. The development of new anticandidosics could be based on the use of molecular motifs known for their anti-infective activities, combining them judiciously in accordance with the principle of juxtaposition of bioactive entities. One of these motifs is imidazo[1,2-a]pyridine, which is an aromatic heterobicyclic compound with angular nitrogen resulting from the "type a" binding between pyridine and imidazole. This heterocycle is well known for its many biological properties including anti-inflammatory [12] anticancer [13], antiplasmodial [14], nematocid [14], antibacterial [15] and antifungal [16] [17]. According to the juxtaposition of bioactive moiety, the arylpropenone named also chalcone sequence was associated with the imidazo[1,2-a]pyridine scaffold. They are also well-known for their multiple anti-infective activities such as antimicrobial [18], antimalarial [19], antifungal [20], anticancer [21], anti-tuberculosis [22]. In most of cases, work already done by others was carried out on chalcones vectorized by benzimidazole, bioisostere of imidazopyridine. However, these imidazopyridinyl-chalcones have shown only nematocidal activity [23]. Another possible approach could to be used is retrochalcones, which have shown good cytotoxic activity [24]. Conventional methods of imidazo[1,2-a]pyridines syntheses proceeded from the condensation reaction of the α-bromocarbonyl compounds with 2-aminopyridine derivatives under neutral basic conditions with solvent and catalysis. Imidazo[1,2-a]pyridine derivatives were also synthesized by solid support, using catalyst such as Al_2O_3 and $TiCl_4$. Even if, these methods are suitable with good yields, they present certain drawbacks such as hazardous organic solvents, high cost, long reaction time, and even excess amounts of reagents or catalysts, special apparatus and drastic reaction conditions. For these reasons, we explored in our work, the synthesizes of various imidazo[1,2-a]pyridine-supported retrochalcones and evaluated their antifungal activity on *C. albicans*.

2. Material and Methods

2.1. Chemistry

2.1.1. Chemistry Materials

All reagents and solvents were obtained from commercial suppliers and were used as is it. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance III spectrometer (400 and 300 MHz for 1H and 101 and 75 MHz for 13C respectively in CDC13 and DMSO-d6) at ambient temperature. Tetramethylsilane (TMS) is used as a reference and chemical displacements are expressed in part per mil-

lion (ppm) while the coupling constants (*J*) are expressed in Hertz (Hz). The multiplicity of signals is represented by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublet). The molecular weights were determined by high-resolution mass spectrometry (HRMS) with electrospray mode (ESI). The reaction progress and the purity of the compounds were checked by TLC on aluminum plates coated with silica gel (Kieselgel 60 F254, MERCK). The plates are revealed by UV fluorescence (λ = 254 nm) or by a solution of $KMnO_4$ followed by heating. The reaction crudes were purified by silica gel chromatography (Kieselgel SI60, 40 - 63). The melting points of the solid compounds were determined using a Köfler bench with a maximum temperature of 266˚C.

2.1.2. Biology Materials

The evaluation of antifungal activity was carried out at the Laboratory of Parasitology and Mycology of the Center for Diagnosis and Research on AIDS and other infectious diseases (CeDReS) in Côte d'Ivoire. The fungus support was made up of a strain of Candida albicans resistant to fluconazole. This clinical strain of *C. albicans* comes from the CeDReS collection. Culture of the strain was carried out on the agar of Sabouraud glucosee (Sabouraud 4% glucose agar, Fluka). The tested compound were ten derivatives of 3-imidazo[1,2-a]pyridinyl-1-arylpropenone (11a - j). The solvents used to solubilize chemicals are dimethyl sulfoxide (DMSO) and distilled water.

2.2. Methods

2.2.1. Methods of Chemistry

General method synthesis of compounds* 3*a*, *b

In a 25 ml round bottom flask, 25 mmol (1 eq) of phenacyl was added, then 25 mmol (1 eq) of 5-chloro-2-aminopyridine also. The mixture was heated to 60˚C and stirred during 30 min. The precipitate formed was washed with acetone. The resulting residue was purified by silica column chromatography gel (hexane/DCM: (70/30)).

2-*phenyl-H-imidazo*[1,2-*a*]*pyridine* (3*a*)

Yellow cristals, yield = 86%, m.p = 133˚C - 135˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 (dt, J = 6.7, 1.0 Hz, $1H_{Ar}$), 7.95 (dt, J = 3.0, 1.8 Hz, $2H_{Ar}$), 7.82 (s, 1H, H_3), 7.62 (dd, J = 9.1, 0.5 Hz, 1HAr), 7.48 - 7.38 (m, $2H_{Ar}$), 7.36 - 7.28 (m, $1H_{Ar}$), 7.14 (ddd, J = 9.1, 6.8, 1.2 Hz, $1H_{Ar}$), 6.73 (td, J = 6.8, 1.0 Hz, $1H_{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.79, 145.69, 133.78, 128.74, 127.98, 126.06, 125.61, 124.66, 117.53, 112.41, 108.15.

6-*chloro*-2-*phenyl-H-imidazo*[1,2-*a*]*pyridine* (3*b*)

Yellow cristals, yield = 90%, m.p = 135˚C - 136˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (d, J = 1.5 Hz, $1H_{Ar}$), 7.94 (dt, J = 3.1, 1.9 Hz, $2H_{Ar}$), 7.81 (s, $1H_{Ar}$, H_3), 7.58 (d, J = 9.6 Hz, $1H_{Ar}$), 7.49 - 7.42 (m, $2H_{Ar}$), 7.39 - 7.33 (m, $1H_{Ar}$), 7.14 (dd, J = 9.6, 2.0 Hz, $1H_{Ar}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.84, 144.05, 133.29, 128.92, 128.30, 126.07, 126.03, 123.38, 120.53, 117.84, 108.51.

***Synthesis method of* 2-*chloro*-*H*-*imidazo*[1,2-*a*]*pyridine* 7**

32.86 mmol (1 eq) of 2-(2-iminopyridinyl)acetic acid was dissolved in 15 mL of toluene. To this solution, 131.45 mmol (4 eq) of $POCl_3$ were dropwise added then the mixture was carried out under reflux for 16 hours. Then, 10 mL of water were added and the mixture was stirred at room temperature for 15 min. In an ice water bath, the reaction medium was neutralized with a 10% NaOH solution. The residue was extracted with DCM and then the organic layer was washed with a saturated NaCl solution. Then, it was dried with anhydrous $MgSO_4$, evaporated in *vacuo*, a crude was obtained and purified by silica gel chromatography (hexane/ethyl acetate: 60/40). White crystals, yield = 85%, m.p = 74˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.07 (d, J = 6.8 Hz, $1H_{Ar}$), 7.56 d, J = 9.1 Hz, $1H_{Ar}$), 7.52 (s, $1H_{Ar,}$ H_3), 7.27 - 7.20 (m, $1H_{Ar}$), 6.86 (t, J = 6.8 Hz, $1H_{Ar}$) ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 125.19, 117.13, 113.06

General method synthesis of compounds* 8*a, b

2.3 mmol (2.3 eq) of $POCl_3$ was added to 1.5 mL of DMF solution at 0˚C. The mixture was allowed to stay at room temperature under magnetic agitation for 15 minutes. After the discoloring of the mixture, 1 mol (1 eq) of imidazo[1,2-a]pyridine (1a or 1b) was added. Then, the temperature was increased to 80˚C for 5 hours. After that time, the medium was neutralized with a saturated sodium hydrogenocarbonate ($NaHCO_3$) solution. The residue was extracted with DCM. The organic layer was dried with sodium sulfate (Na_2SO_4), filtered and purified by silica gel chromatography (Hexane/ethyl acetate: 80/20).

2-*phenyl*-*H*-*imidazo*[1,2-*a*]*pyridine*-3-*carbaldehyde* (8*a*)

White crystals, yield = 71%, m.p = 159˚C - 161˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.10 (s, 1H, CH = O), 9.70 (dt, J = 6.8, 1.1 Hz, 1H, HAr), 7.86 (dd, J = 7.4, 5.4, 2.1 Hz, 3H, H_{Ar}), 7.65 - 7.52 (m, 4H, H_{Ar}), 7.16 (td, J = 6.9, 1.1 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 179.64, 158.37, 147.78, 132.39, 130.44, 129.86, 128.92, 128.85, 120.78, 117.48, 115.32.

6-*chloro*-2-*phenyl*-*H*-*imidazo*[1,2-*a*]*pyridine*-3-*carbaldehyde* (8*b*)

Yellow crystals, yield = 80%, m.p = 150˚C - 152˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.10 (s, 1H, CH = O), 9.80 - 9.76 (m, 1H, H_{Ar}), 7.86 (d, J = 4.2 Hz, 1H, H_{Ar}), 7.84 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.78 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.60 (d, J = 2.1 Hz, 1H, H_{Ar}), 7.59 - 7.54 (m, 3H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 179.75, 158.40, 146.02, 131.97, 131.58, 130.09, 129.77, 129.01, 126.78, 123.54, 120.84, 117.67.

***Synthesis method of* 2-*chloro*-*H*-*imidazo*[1,2-*a*]*pyridine*-3-*carbaldehyde* (8*c*)**

In a round bottom flask containing 1.5 mL of DMF, 2.3 mmol (2.3 eq) of $POCl_3$ were dropwise added at 5˚C. The mixture was left at room temperature under magnetic agitation for 15 minutes. After discoloration of the solution, 1 mmol (1 eq) of 2-chloroimidazo[1,2-a]pyridine (7) was added. The mixture was kept at room temperature for 2 hours. The reaction medium was spilled into ice water and a precipitate was formed and filtered. The resulting residue was dissolved and extracted with DCM. The organic layer was dried with Na_2SO_4 and filtered. The crude was purified by silica gel chromatography (Hexane/ethyl acetate:

70/30). White crystals, yield = 85%, m.p = 120˚C - 122˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.99 (s, 1H, CH = O), 9.49 (dt, J = 6.8, 1.1 Hz, 1H, H_{Ar}), 7.71 (dd, J = 9.0, 1.0 Hz, 1H, H_{Ar}), 7.65 - 7.57 (m, 1H, H_{Ar}), 7.18 (td, J = 6.9, 1.2 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.21, 147.51, 146.25, 130.92, 128.09, 118.79, 117.07, 116.03.

General method of synthesis of compounds* 10*a-j

In a round bottom flask containing 5 mL of terbutanol, acetophenone derivatives (9a - e) (1.1 mmol, 1 eq), a sodium hydroxide (NaOH) solution (8.25 mmol, 7.5eq dissolved previously in 2 mL of water) were added and stirred under magnetic agitation for 15 min. The imidazo[1,2-a]pyridine-3-carbaldehyde derivative (8a - c) (1.1 mmol, 1 eq) was then added to the mixture and left at room temperature under magnetic agitation for 8 h. The reaction medium was neutralized with a solution of acetic acid (20%). A precipitate was formed, filtered and dried. The product was purified on silica gel (hexane/ethyl acetate (90/10)).

1-(2-*hydroxyphenyl*)-3-(2-*phényl-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)*prop*-2-*en*-1-*one* (10*a*)

Yellow crystals, yield = 65%, m.p = 100˚C - 102˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.54 (d, J = 6.9 Hz, 1H, H_{Ar}), 8.28 (d, J = 15.5 Hz, 1H, H_3), 7.84 - 7.74 (m, 3H, 2H_{Ar} et H_2), 7.62 (dd, J = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.59 - 7.37 (m, 6H, H_{Ar}), 7.09 (td, J = 6.9, 1.2 Hz, 1H, H_{Ar}), 7.00 (dd, J = 8.4, 1.0 Hz, 1H, H_{Ar}), 6.93 - 6.82 (m, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 193.06, 163.64, 152.70, 147.79, 136.25, 133.99, 130.41, 129.66, 129.35, 129.20, 129.00, 127.55, 125.39, 120.21, 118.92, 118.77, 118.53, 115.33, 114.56.

1-(4-*methoxyphényl*)-3-(2-*phenyl-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)*prop*-2-*en*-1-*one* (10*b*)

Yellow crystals, yield = 60%, m.p = 112˚C - 114˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.54 (d, J = 6.9 Hz, 1H, H_{Ar}), 8.20 (d, J = 15.7 Hz, 1H, H_3), 7.95 (t, J = 10.2 Hz, 2H, H_{Ar}), 7.87 - 7.73 (m, 3H, 2 H_{Ar} et H_2), 7.59 - 7.45 (m, 4H, H_{Ar}), 7.40 (dd, J = 8.3 Hz, 1H, H_{Ar}), 7.06 (dd, J = 6.9, 5.9 Hz, 1H, H_{Ar}), 6.95 (dd, J = 9.2, 2.3 Hz, 2H, H_{Ar}), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 187.96, 163.39, 134.11, 131.17, 130.59, 129.51, 129.14, 128.95, 128.80, 126.78, 125.15, 118.32, 117.80, 114.04, 113.88, 55.52.

3-(6-*chloro*-2-*phenyl-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-*phenylprop*-2-*en*-1-*one* (10*c*)

Yellow crystals, yield = 73%, m.p = 150˚C - 152˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.54 (d, J = 1.2 Hz, 1H, H_{Ar}), 8.14 (d, J = 15.8 Hz, 1H, H_3), 7.91 (dd, J = 5.2, 3.3 Hz, 2H, H_{Ar}), 7.78 (dd, J = 4.9, 2.9 Hz, 1H, H_{Ar}), 7.74 (d, J = 15.8 Hz, 1H, H_2), 7.72 - 7.66 (m, 1H, H_{Ar}), 7.60 - 7.44 (m, 7H, H_{Ar}), 7.35 (dd, J = 9.5, 2.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 189.51, 151.88, 145.54, 138.05, 133.60, 132.92, 129.42, 129.29, 129.24, 128.89, 128.73, 128.35, 128.07, 125.79, 123.10, 122.41, 118.84, 118.57.

3-(6-*chloro*-2-*phenyl-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-(2-*hydroxyphenyl*)*prop*-2-*en*-1-*one* (10*d*)

Orange crystals, yield = 75%, m.p = 196˚C - 198˚C. ^{1}H NMR (300 MHz, $CDCl_3$)

δ (ppm) 8.54 (d, J = 1.2 Hz, 1H, H_{Ar}), 8.21 (d, J = 15.6 Hz, 1H, H_3), 7.81 - 7.68 (m, 3H, 2 H_{Ar} et H_2), 7.63 - 7.45 (m, 6H, H_{Ar}), 7.39 (dd, J = 9.5, 1.9 Hz, 1H, H_{Ar}), 7.05 - 6.99 (m, 1H, H_{Ar}), 6.94 - 6.86 (m, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 192.82, 163.59, 152.46, 145.74, 136.36, 133.57, 129.51, 129.42, 129.14, 128.96, 128.41, 122.99, 122.64, 119.98, 118.91, 118.71, 118.66, 116.80.

1-(4-*aminophenyl*)-3-(6-*chloro*-2-*phenylH-imidazo*[1,2-*a*]*pyridin*-3-*yl*)*prop*-2-*en*-1-*one* (10*e*)

Yellow crystals, yield = 75%, m.p = 210˚C - 212˚C. ^{1}H NMR (300 MHz, DMSO-*d*6) δ (ppm) 9.10 (d, J = 1.2 Hz, 1H, H_{Ar}), 7.94 (d, J = 15.8 Hz, 1H, H_3), 7.88 - 7.79 (m, 3H, H_{Ar}), 7.78 - 7.69 (m, 3H, 2 H_{Ar} et H_2), 7.64 - 7.48 (m, 4H, H_{Ar}), 6.62 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.16 (s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-*d6*) δ (ppm) 186.02, 154.32, 150.51, 145.20, 134.18, 131.55, 129.67, 129.24, 128.43, 127.08, 125.74, 125.42, 121.52, 120.42, 119.25, 118.42, 113.15.

3-(2-*chloro-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-*phenylprop*-2-*en*-1-*one* (10*f*)

Yellow crystals, yield = 94%, m.p = 189˚C - 191˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.54 (d, J = 6.9 Hz, 1H, H_{Ar}), 8.28 (d, J = 15.5 Hz, 1H, H_3), 7.84 - 7.74 (m, 3H, 2 H_{Ar} et H_2), 7.62 (dd, J = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.59 - 7.37 (m, 6H, H_{Ar}), 7.09 (td, J = 6.9, 1.2 Hz, 1H, H_{Ar}), 7.00 (dd, J = 8.4, 1.0 Hz, 1H, H_{Ar}), 6.93 - 6.82 (m, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 193.06, 163.64, 152.70, 147.79, 136.25, 133.99, 130.41, 129.66, 129.35, 129.20, 129.00, 127.55, 125.39, 120.21, 118.92, 118.77, 118.53, 115.33, 114.56.

3-(2-*chloro-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-(2-*hydroxyphenyl*)*prop*-2-*en*-1-*one* (10*g*)

Orange crystals, yield = 81%, m.p = 234˚C - 236˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.39 (d, J = 7.0 Hz, 1H, H_{Ar}), 8.16 (d, J = 15.4 Hz, 1H, H_3), 8.01 (d, J = 15.4 Hz, 1H, H_2), 7.93 (dd, J = 8.1, 1.5 Hz, 1H, H_{Ar}), 7.66 (d, J = 9.0 Hz, 1H, H_{Ar}), 7.56 - 7.40 (m, 2H, H_{Ar}), 7.16 - 6.94 (m, 3H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 193.03, 163.64, 136.47, 129.46, 127.82, 126.49, 123.90, 119.03, 118.68, 117.85, 117.14, 114.78.

3-(2-*chloro-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-(4-*methoxyphenyl*)*prop*-2-*en*-1-*one* (10*h*)

Yellow crystals, yield = 95%, m.p = 202˚C - 204˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.36 (d, J = 6.6 Hz, 1H, H_{Ar}), 8.14 - 8.00 (m, 3H, 2 H_{Ar} et H_3), 7.92 (d, J = 15.6 Hz, 1H, H_2), 7.63 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.45 - 7.34 (m, 1H, H_{Ar}), 7.07 (d, J = 6.5 Hz, 1H, H_{Ar}), 7.00 (d, J = 8.6 Hz, 2H, H_{Ar}), 3.90 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 187.82, 163.59, 144.89, 131.04, 130.78, 127.23, 125.27, 123.85, 119.17, 117.68, 116.95, 114.43, 113.97, 55.55.

3-(2-*chloro-H-imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-(4-*aminophenyl*)*prop*-2-*en*-1-*one* (10*i*)

Yellow crystals, yield = 88%, m.p = 264˚C - 266˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.98 (d, J = 6.9 Hz, 1H, H_{Ar}), 7.98 - 7.88 (m, 3H, 2 H_{Ar} et H_3), 7.84 (d, J = 15.8 Hz, 1H, H_2), 7.71 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.62 - 7.51 (m, 1H, H_{Ar}), 7.23 (td, J = 6.9, 1.1 Hz, 1H, H_{Ar}), 6.65 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.19 (s, 2H, NH_2); ^{13}C

NMR (75 MHz, $CDCl_3$) δ (ppm) 185.67, 154.40, 144.92, 139.04, 131.46, 128.57, 127.17, 125.70, 124.70, 118.79, 117.11, 116.99, 115.26, 113.27.

3-(2-*chloro*-*H*-*imidazo*[1,2-*a*]*pyridin*-3-*yl*)-1-(4-*fluorophenyl*)*prop*-2-*en*-1-*one* (10*j*)

Yellow crystals, yield = 90%, m.p = 208˚C - 210˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.37 (d, J = 6.9 Hz, 1H, H_{Ar}), 8.15 - 8.04 (m, 3H, 2 H_{Ar} et H_3), 7.89 (d, J = 15.5 Hz, 1H, H_2), 7.68 - 7.62 (m, 1H, H_{Ar}), 7.24 (dd, J = 7.0, 4.2 Hz, 1H, H_{Ar}), 7.18 (dd, J = 6.8, 4.8 Hz, 1H, H_{Ar}), 7.09 (td, J = 6.9, 1.2 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 187.88, 145.11, 139.79, 131.10, 130.98, 127.52, 126.18, 123.86, 118.44, 117.78, 116.02, 115.73, 114.61.

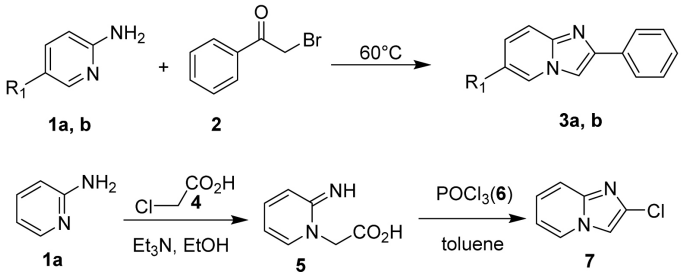
2.2.2. Methods of Biology

The antifungal activity of 3-imidazo[1,2-a]pyridinyl-1-arylpropenone derivatives (10a - j) was determined by the measurement of the minimum inhibitory concentration (MIC) using the microdilution method. This method consists to put in contact a *Candida* inoculum with an increasing dilution of antifungal in microplates of 96 wells. Practically, a culture of the strain was carried out on Sabouraud agar (Sabouraud 4% glucose agar, Fluka) in a *Petri dish* and incubated at 30˚C for 48 hours. A colony was seeded in 50 mL of Brain Heart Broth (BHB) and left under agitation overnight at room temperature. One (1) mL of the broth containing the fungus was transferred to 50 mL of sterile broth. This BHB was then left under agitation for 6 hours (time needed to achieve exponential growth of *Candida sp*). At the time of the test, 5 mL of approximately 6-hour BTS was added to 50 mL of sterile BTS to obtain an inoculum containing approximately 10^5 cells/mL. In practice, the plates were incubated at 30˚C for 48 hours. To reveal the microplates thus prepared, 40 µL of a solution of Methyl chloride Thiazolyl Tetrazolium (MTT) were prepared in DMSO at the concentration of 2.5 mg/mL and distributed in the wells and incubated for another 30 min at room temperature. The inoculum containing approximately 10^5 cells/mL was based on the principle of the "agar overlay" bioautography technique [25].

3. Results and Discussion

3.1. Chemistry

The 2-substituted imidazo[1,2-a]pyridines (3a - b and **7**) were obtained using the synthesis pathway described in **Scheme 1**. Firstable, phenacyl (2) reacted with 2-aminopyridine (1a) or 2-amino-5-chloropyridine (1b) by a solvent-free fusion reaction at 60˚C to form 2-amino-5-chloropyridinephenylimidazo[1,2-a] pyridine (3a - b) as described by Zhu *et al.* [26]. Then, in two reactive steps, 2-chloroimidazo[1,2-a]pyridine (**7**) was obtained with a yield of 80% *via* the method described by Maxwell *et al.* [27]. In the first step, 2-aminopyridine 1a was in reaction with chloroacetic acid (4) under reflux in ethanol with the presence of triethylamine (Et_3N) yielded to 2-(2-iminopyridinyl) acetic acid (**5**). The second step consisted of an intramolecular cyclization of the intermediate (**5**) using phosphoryl trichloride ($POCl_3$) in toluene. Compounds 3a - b and **7** undergo a



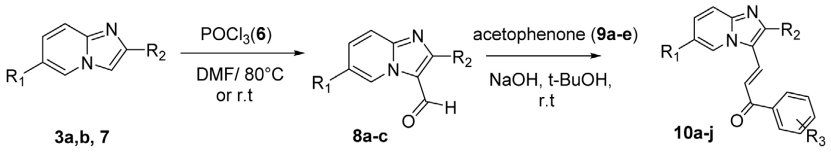
Scheme 1. Synthesis route of 2-phenyl-*H*-imidazo[1,2-a]pyridine (3a - b) and 2-chloro-*H*-imidazo[1,2-a]pyridine (**7**).

Vilsmeier-Haack formylation reaction to give the imidazopyridine-3-carbaldehyde derivatives (8a - c). Finally, these aldehydes reacted with the acetophenone derivatives (9a - e) in a Claisen-Schmidt condensation reaction in basic medium yielded in 60% to 95% to give 3-imidazo[1,2-a]pyridinyl-1-arylpropenone derivatives (10a - j) (Scheme 2). Formation of 3-imidazo[1,2-a] pyridinyl-1-arylpropenone derivatives (10a-j) could be justified by the loss of the 9.99 ppm signal attributed to the aldehyde proton (CH=O) and the appearance of two doublets, one around 8.16 and the other one around 8.01 ppm. These doublets are attributable to the two *α*, *β*-ethylene protons (CH=CH). Additionally, deuce different coupling constants of 15.4 Hz and 15.8 Hz between the two protons allowed us to speculate that 10a - d derivatives synthesized are presented such as in *trans*-configuration.

3.2. Biology

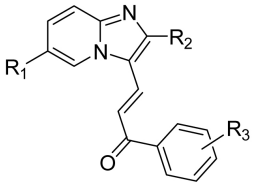
The compounds 10a - j were evaluated for their antifungal activity against *Candida albicans*. Their minimum inhibitory concentrations (MICs) are summarized in Table 1 below.

To investigate the antifungal activity of 3-imidazo[1,2-a]pyridinyl-1-arylpropenone derivatives (10a - d), a first series of compounds with phenyl at the 2-position of imidazopyridine compound, placed there the intention to provide a stability to the molecule, was studied. These compounds 10a and 10b, carriers of hydroxyl and methoxy function on the phenyl scaffold of acetophenone derivatives. However, these compounds showed CMIs greater than 300 or equal to 282.17 µmol/L, respectively. The addition of a chlorine atom, known for its modulation properties, at the 6-position, led to a second series of three compounds, two of them **10c** and **10d** gave MIC values of 139.35 and 268.02 µmol/L respectively. On compound **10e**, the replacement of the hydroxyl function at the -2 position by the amino function at the -4 position resulted in a decrease of antifungal potency. Given the interest of the chlorine atom, a final series of structural variations has been undertaken, thus consisting of the introduction at the 2-position chlorine atom on imidazo[1,2-a]pyridine scaffold. This structural variation resulted in an overall loss of antifungal potency, with an exception for compound 10i, which has a 4-position amino function on the phenyl. Indeed, this compound was the most potent with a MIC value of 41.92 µmol/L.



Scheme 2. Synthesis route of 3-imidazo[1,2-a]pyridinyl-1-arylpropenone (10a - j).

Table 1. MIC (μmol/L) of 3-imidazo[1,2-a]pyridinyl-1-arylpropénone derivatives (10a - j).

Compounds	General Structure	R_1	R_2	R_3	MICs (μmol/L)
10a		H	C_6H_5	2-OH	>300
10b		H	C_6H_5	4-OCH_3	282.17
10c		Cl	C_6H_5	H	139.35
10d		Cl	C_6H_5	2-OH	268.02
10e		Cl	C_6H_5	4-NH_2	>300
10f		H	Cl	H	>300
10g		H	Cl	2-OH	>300
10h		H	Cl	4-OCH_3	>300
10i		H	Cl	4-NH_2	41.98
10j		H	Cl	4-F	>300

4. Conclusion

Our recent work has identified ten (10) 3-imidazo[1,2-a]pyridinyl-1-arylpropenone derivatives as pharmacophore and characterized them by ^{1}H and ^{13}C NMR spectroscopy and HRMS spectrometry. The study of the antifungal activity of these compounds was carried out against *Candida albicans* strain. We find that the choice of the hybride 3-imidazo[1,2-a]pyridinylarylpropenone or 3-imidazo[1,2-a]pyridinylchalcone scaffold is judicious as a novel pharmacophore with an interesting antifungal potential. These results with regard to *Candida albicans*, a strain resistant to fluconazole, opens novel way of investigation towards the development of new scaffolds that have an antifungal potential capable of overcoming antifungal resistances.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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