



Synthesis and Anticandidal Activity of New 6-Chloroimidazo[1,2-a]pyridine Derivatives

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The general objective assigned to this work was to contribute to the pharmacochemical development of new antifungal drugs derived from 6-Chloroimidazo [1,2-a]pyridine. This preliminary study was conducted on *Candida parapsilosis*, which is an increasingly difficult organism to treat.

Methodology: The imidazo [1,2-a] pyridinylacrylonitriles designed by juxtaposition of bioactive entities were synthesized in three steps. Firstly, this involves the synthesis of the imidazopyridine core via cyclocondensation. Then, its functionalization at position 2 with an acetonitrile group, and finally condensation of the resulting intermediate with various aromatic aldehydes

Results: A total of ten derivatives of (6-chloroimidazo [1,2-a]pyridin-2-yl)-phenylacrylonitrile were obtained, with yields ranging from 63% to 92%. The biological evaluation focused on the antifungal activity of these compounds against a clinical strain of *Candida parapsilosis*, with minimum inhibitory concentrations (MIC) ranging from 19.36 μ M to 89.38 μ M. Structure–activity relationship (SAR) analysis revealed that the nature and position of the substituent on the aryl ring significantly modulate antifungal efficacy. These findings highlight the pharmacochemical relevance of electron-withdrawing or polarizable substituents in enhancing antifungal activity.

Conclusion: Due to their innovative profile combining a functional chain and a bioactive pharmacophore, these novel imidazo[1,2-a]pyridine hybrids appear as promising candidates for the development of potent antifungal agents, particularly against *Candida* species.

Keywords: Imidazo[1,2-a]pyridine; Acrylonitrile; anticandidosis; antiinfective.

1. INTRODUCTION

Opportunistic fungal infections, particularly those caused by *Candida* species, represent a major public health problem, especially in immunocompromised, transplanted, or HIV patients (Seagle et al., 2021). Fungal diseases affect more than one billion people annually and cause approximately 1.5 million deaths worldwide (Bongomin et al., 2017). Among them, invasive *Candida* spp. infections are of particular concern because they are associated with severe morbidity and represent nearly 30% of global mortality related to mycoses (Strollo et al., 2016). Among these species, *Candida albicans*, *Candida tropicalis* and *Candida glabrata* are responsible for severe systemic candidiasis (Katsipoulaki et al., 2024). Apart from these *Candida* species, other non-*albicans* species, such as *Candida parapsilosis*, seem to be gaining importance in the etiology of candidemia (Won et al., 2024). Indeed, according to A. Paugam et al., *C. parapsilosis* candidemia is associated with two main factors: broad-spectrum antibiotic therapy and prior treatment with caspofungin (Paugam et al., 2011). They reported that the emergence of *C. parapsilosis* candidemia appears to coincide with the introduction of caspofungin, suggesting a possible association with its level of use in intensive care (Paugam et al., 2011). *C. parapsilosis* infections constitute a growing threat to public health. Therefore, the search for new agents active against *Candida parapsilosis* is

considered urgent by the WHO because this germ is on the list of priority pathogens (Asogan et al., 2024; Claridge, 2016).

Although several antifungals are available on the market, such as polyenes, echinocandins and azoles, the emergence of multiple resistances compromises their efficacy and justifies the urgent search for new classes of active molecules (Boan&Gardam, 2019); Asadzadeh et al., 2017; Ben-Ami & Kontoyiannis, 2021). In this perspective, medicinal chemistry research has focused on the design of hybrid structures combining pharmacophore motifs known for their anti-infectious activity (Viegas-Junior et al., 2007). It is in this context that our team has focused on the imidazo[1,2-a]pyridine heterocycle, a diazole bioisostere of benzimidazole, known for its wide range of biological activities, including antifungal, antiparasitic and anticancer properties (N'Guessan et al., 2017; N'Guessan et al., 2021; Peytam et al., 2023).

On the other hand, the acrylonitrile group, by its α,β -unsaturated electrophilic nature, is a Michael acceptor capable of interacting covalently with the thiol residues of certain target proteins (Fleming et al., 2010; Krishnan et al., 2014; Sutton et al., 2024; Koo et al., 2023). This chemical fragment is already present in many anti-infective drugs, such as rilpivirine (antiretroviral) and neratinib (anticancer), and has demonstrated a remarkable ability to

potentiate the biological activity of the heterocycles to which it is grafted (Deeks, 2017; Chounta et al., 2021). In a previous study, we designed new imidazopyridinyl-acrylonitrile derivatives that could exhibit strong antifungal activity, particularly against resistant clinical strains of *Candida* (N'Guessan et al., 2021). Preliminary data revealed promising profiles, with some compounds surpassing fluconazole, the reference molecule, in terms of activity against *C. tropicalis*, *C. glabrata* and *C. albicans* (N'Guessan et al., 2021). The 3-chlorinated derivative proved to be the most effective, regardless of the *Candida* species considered. Structure-activity relationship (SAR) analysis also identified key groups (Cl) that significantly enhance antifungal activity (N'Guessan et al., 2021). Furthermore, chlorine has demonstrated its ability to boost the antifungal activities of many currently marketed drugs, particularly those in the azole antifungal class (ketoconazole, econazole, isoconazole, miconazole, etc.). Therefore, It was opportune to study its impact on a series of imidazopyridine-based derivatives, which, like the imidazole nucleus, is a diazaheteroaryl. In this study, we developed 6-chloro derivatives of imidazo[1,2-*a*]pyridinylphenylacrylonitriles for anticandidal purposes.

To this end, we undertook to evaluate the antifungal activity of these synthetic compounds against *Candida parapsislosis*. The results of such a study could pave the way for the development of new anticandidal molecules capable of circumventing growing fungal drug

resistance and strengthening the current therapeutic arsenal.

2. METHODOLOGY

2.1 General Considerations

The progress of the reactions was monitored by thin layer chromatography (TLC) on aluminum plates coated using Merk® silica gel 60F₂₅₄ plates. The revelation was done with UV light ($\lambda = 254$ nm) with a mixture of ethyl acetate and hexane (70:30) as eluent. NMR experiments were performed at 300.13 MHz (¹H) and 75.46 MHz (¹³C) on a Bruker-Avance 300 MHz spectrometer. Chemical shifts (δ) are measured in parts per million (ppm) using tetramethylsilane as the internal reference solvent.

At the residual signal of chloroform (7.26 ppm for proton NMR, 77.16 ppm for carbon NMR) for spectra carried out in deuterated chloroform (CDCl₃), at the residual signal of dimethyl sulfoxide (2.50 ppm for proton NMR and 39.52 ppm in carbon NMR) for spectra carried out in dimethyl sulfoxide hexadeuterated (DMSO-d₆).

The coupling constants (*J*) are expressed in Hertz (Hz) and the multiplicity of the signals is described as follows: singlet (s), wide singlet (sl), doublet (d), doublet of doublet (dd), split doublet of doublet (ddd), triplet of doublet (td), quadruplet (q) and multiplet (m). Melting points of the compounds were determined on a K f ler bench and are uncorrected.

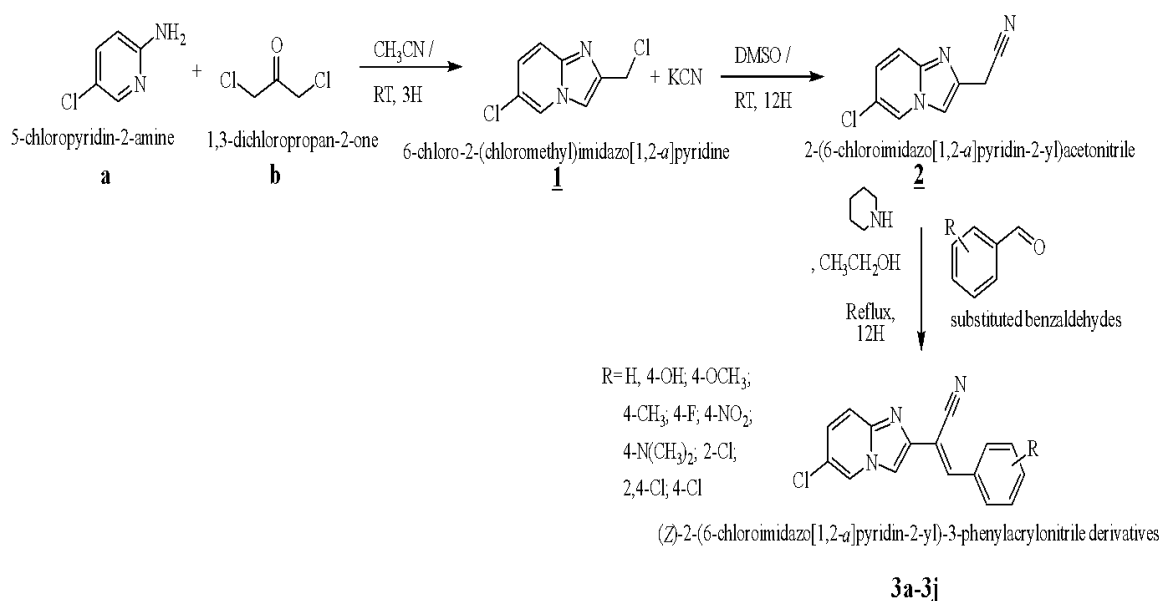


Fig. 1. Synthesis of proposed imidazo[1,2-*a*]pyridinehybrid derivatives

2.2 Synthesis of 6-Chloro-2-(chloromethyl) Imidazo[1,2-a] Pyridine

The imidazo[1,2-a]pyridinylacrylonitriles, were synthesized in 3 steps. This involves first of all the construction of the imidazopyridine core by cyclocondensation, then its functionalization in position 2 by the acetonitrile group and finally the condensation of this intermediate with an aromatic aldehyde. Formation of the imidazo[1,2-a]pyridine ring resulted in the formation of 6-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine1. Indeed, this synthesis which follows the classical scheme was carried out by condensation of 5-chloro-2-aminopyridine and 1,2-dichloroacetone. On the other hand, various approaches in the literature have been addressed, using solvents such as DMF (Sissouma et al., 2011), ethyl acetate (Kovalenko et al., 2002), ethanol (Endoori et al., 2020) and methanol (Kutrov et al., 2008). For our study, we opted for acetonitrile as the reaction medium (Fig. 1).

Once the core is formed, the next step is to synthesize the acetonitrile intermediate, 2-(imidazo[1,2-a]pyridin-2-yl)acetonitrile 2, which would promote condensation.

2.2.1 Method for synthesis of 2-chloromethyl imidazo[1, 2-a]pyridine

To a solution of 2.35 g (24.9 mmol, 1 eq) of 2-amino-4-chloropyridine in 25 ml of acetonitrile, are added and 3.2 g (25.2 mmol, 1.01 eq) of 1,3-dichloroacetone. The mixture is left stirring at room temperature for 12 hours. The precipitate formed is isolated by vacuum filtration, washed 2 times with 15 ml of acetonitrile, drained and then dried at room temperature. The residue is then dissolved in 60 ml of water and the solution is neutralized with a saturated solution of sodium hydrogen carbonate (NaHCO_3). The impurities are extracted from the mixture with 2 times 15 ml of ethyl acetate, then the aqueous phase is stored in the refrigerator (5°C) and the product precipitates after one hour. After vacuum filtration, the product is isolated as a white flaky solid, with a yield of 49.28%.

2.3 Synthesis of 2-(6-chloroimidazo [1,2-a]pyridin-2-yl) Acetonitrile

2-(6-chloroimidazo[1,2-a]pyridin-2-yl)acetonitrile 2 was prepared by the cyanation of 6-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine 1 using potassium cyanide. The reaction takes place in dimethyl sulfoxide (DMSO) at room temperature (Fig. 1).

2.3.1 Method for synthesis of 2-(6-chloroimidazo[1,2-a]pyridin-2-yl)acetonitrile

A mixture of 2-chloromethyl imidazo[1,2-a]pyridine(1g; 6 mmol; 1eq) and potassium cyanide (0.43; 6.6 mmol; 1.1 eq) was stirred for 12 h at room temperature in a 100 ml flask containing 10 ml of DMSO. The brown liquid was extracted with dichloromethane (2 x 50 ml), then washed 2 times with 50 ml of water. The organic phase was dried over magnesium sulfate, filtered and concentrated under vacuum. The brown paste formed crystallized after 30 minutes at room temperature, with a yield of 87.23%.

2.4 Synthesis of (Z)-2-(6-chloroimidazo[1,2-a] pyridin-2-yl)-3-phenylacrylonitrile derivatives

This is the reaction of an activated methylene with aromatic aldehydes. The method used consists of treating compound 2 and benzaldehyde substituted or not in a hot medium, in presence of piperidine. We obtained phenylacrylonitrile derivatives with imidazo[1,2-a]pyridine support compounds 3a-3j (Fig. 1).

2.4.1 General method of synthesis of imidazo[1,2-a]pyridine phenylacrylonitrile

To a solution of 0.5 g (3.18 mmol; 1 eq) of 2-(imidazo[1,2-a]pyridin-2-yl)acetonitrile in 8 ml of anhydrous ethanol, 5 drops of piperidine and 3.2 g (3.5 mmol; 1.1 eq) of benzaldehyde are added. The mixture is refluxed for 12 h. The precipitate formed is isolated by vacuum filtration, washed with 10 ml of cold methanol, drained and then dried at room temperature. The product which is the unsubstituted derivative (3a) is isolated in the form of a yellow solid, with a yield of 70%.

The other derivatives with different substituents (4-OH; 4-OCH₃; 4-CH₃; 4-F; 4-NO₂; 4-N(CH₃)₂; 2-Cl; 2,4-Cl; 4-Cl) were obtained using the same method.

2.5 Biology

2.5.1 Microbiological material

To evaluate the antifungal activity of the products, we used a clinical strain of *Candida parapsilosis* (strain 418068) from the parasitology laboratory of the Angré University Hospital, Abidjan, Côte d'Ivoire.

2.5.2 Determination of minimum inhibitory concentrations (MICs) by microplate dilution

The antifungal activity of the compounds was assessed using the microplate dilution method, aiming to determine the minimum inhibitory concentrations (MICs) against *Candida* strains. This technique involves exposing a fungal inoculum to increasing concentrations of test substances in 96-well plates.

The *Candida* inoculum was prepared using the same conditions as those described for the bioautography assay. Stock solutions of imidazo[1,2-a]pyridinylphenylacrylonitrile compounds were prepared at 1 mg/mL in dimethyl sulfoxide (DMSO), then diluted in BTS broth to achieve an initial concentration of 188 µg/mL.

A volume of 188 µL of this solution was distributed into the wells of the first column of the microplate. The remaining wells received 58 µL of BTS broth, followed by a series of two-fold dilutions by transferring 58 µL from one well to the next.

Next, 58 µL of fungal inoculum was added to each well (except the last well, which was used as a sterility control), and the plates were incubated at 30°C for 48 hours.

To detect fungal growth, 48 µL of a 2.5 mg/mL aqueous solution of methylthiazolyltetrazolium chloride (MTT) was added to each well, followed by a 30-minute incubation at room temperature. The color change of the medium, from yellow to purple, indicates cell viability via mitochondrial dehydrogenase activity.

The MIC was defined as the lowest concentration of the compound for which no color change (yellow purple) is observed, indicating complete inhibition of fungal growth.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Chemistry

We obtained 10 compounds derived from 6-chloroimidazo[1,2-a]pyridin-2-yl)-phenylacrylonitrile (**3a** to **3j**) with yields varying between 63 and 92%. These compounds are presented as powder of variable color. To confirm the identity of the ten synthesized (Z)-2-

(6-chloroimidazo[1,2-a]pyridin-2-yl)-3-phenylacrylonitriles. The synthesized compounds were characterized by ¹H and ¹³C NMR. Here NMR analysis data of synthesized imidazo[1,2-a]pyridine derivatives are presented:

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-phenylacrylonitrile (3a): Yield – 70%. M. p. 181–185 °C. Yellow powder. RF = 0.87 cm (Mobile phase: Ethyl Acetate / Hexane, 60:40). ¹H NMR (300 MHz, DMSO-d₆), δ, ppm: 8.87 (1H, dd, J = 2.2, 0.9 Hz, ArH), 8.29 (1H, s, ArH), 8.23 (1H, s, ArH), 8.01–7.93 (2H, m, ArH), 7.69–7.60 (1H, m, ArH), 7.60–7.48 (3H, m, ArH), 7.41 (1H, dd, J = 9.6, 2.1 Hz, ArH). ¹³C NMR (75 MHz, DMSO-d₆), δ, ppm: 144.08, 141.94, 141.37, 133.79, 131.32, 129.60, 127.87, 125.74, 119.97, 117.85, 112.48, 104.21.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-hydroxyphenyl)acrylonitrile (3b): Yield – 63%. M. p. 155–157 °C. Yellow lumpy powder. RF = 0.80 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ¹H NMR (300 MHz, DMSO-d₆), δ, ppm: 8.88–8.83 (1H, m, ArH), 8.23 (1H, s, ArH), 8.16 (1H, s, ArH), 8.02–7.95 (2H, m, ArH), 7.63 (1H, d, J = 9.6 Hz, ArH), 7.39 (1H, dd, J = 9.6, 2.1 Hz, ArH), 7.15–7.09 (2H, m, ArH). ¹³C NMR (75 MHz, DMSO-d₆), δ, ppm: 161.8, 144.0, 141.8, 141.7, 131.7, 127.6, 126.4, 125.6, 119.8, 118.3, 117.7, 115.2, 111.8, 100.9.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (3c): Yield – 65%. M. p. 176–178 °C. Yellow crystalline powder. RF = 0.77 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ¹H NMR (300 MHz, CDCl₃), δ, ppm: 8.16 (1H, d, J = 1.1 Hz, ArH), 8.11 (1H, s, ArH), 7.90 (2H, d, J = 8.6 Hz, ArH), 7.81 (1H, s, ArH), 7.55 (2H, dd, J = 15.1, 9.2 Hz, ArH), 6.95–6.89 (3H, m, ArH), 3.84 (2H, d, J = 8.2 Hz, OCH₃). ¹³C NMR (75 MHz, CDCl₃), δ, ppm: 131.15, 127.12, 126.40, 125.14, 119.80, 118.32, 117.70, 115.15, 111.78.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(p-tolyl)acrylonitrile (3d): Yield – 67%. M. p. 152–154 °C. Yellow crystalline powder. RF = 0.76 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ¹H NMR (300 MHz, CDCl₃), δ, ppm: 8.13–8.10 (1H, m, ArH), 7.93 (1H, dd, J = 1.9, 0.8 Hz, ArH), 7.84–7.77 (1H, m, ArH), 7.54 (1H, d, J = 9.6 Hz, ArH), 7.34 (1H, d, J = 0.4 Hz, ArH), 7.29 (1H, s, ArH), 7.11 (1H, dd, J = 9.6, 2.0 Hz, ArH), 6.97 (2H, d, J = 8.0 Hz, ArH), 5.77 (1H, s, ArH), 2.20 (3H, s, CH₃). ¹³C NMR (75 MHz, CDCl₃), δ, ppm: 142.9, 142.2, 138.3, 130.4, 129.9, 129.6, 129.1,

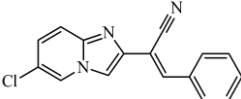
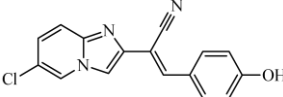
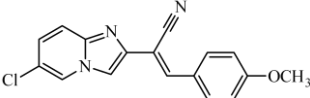
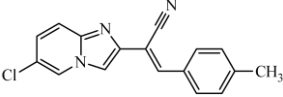
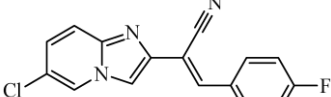
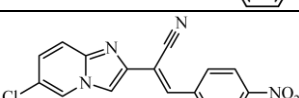
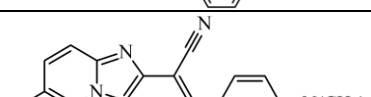
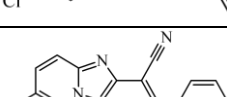
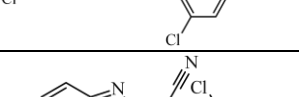
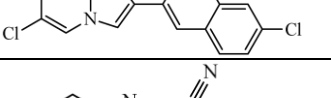
127.7, 126.7, 123.7, 121.2, 118.4, 117.7, 112.2, 111.2, 54.7, 44.5.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-fluorophenyl)acrylonitrile (3e): Yield – 84%. M. p. 196–200 °C. Fine yellow powder. RF = 0.85 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ¹H NMR (300 MHz, CDCl₃), δ, ppm: 8.88–8.84 (1H, m, ArH), 8.40 (1H, s, ArH), 8.35 (1H, s, ArH), 8.13–8.07 (1H, m, ArH), 7.71 (1H, d, J = 9.7 Hz, ArH), 7.68–7.64 (1H, m, ArH), 7.58–7.51 (2H, m, ArH), 7.44 (1H, dd, J = 9.6, 2.2 Hz, ArH). ¹³C NMR (75 MHz, CDCl₃), δ, ppm:

144.5, 141.9, 138.7, 135.3, 132.1, 131.6, 130.2, 129.3, 127.9, 127.3, 123.9, 121.3, 118.2, 116.9, 111.84, 107.1.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-nitrophenyl)acrylonitrile (3f): Yield – 90%. M. p. 204–208 °C. Fine green powder. RF = 0.60 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ¹H NMR (300 MHz, CDCl₃), δ, ppm: 8.86 (1H, dd, J = 2.2, 0.9 Hz, ArH), 8.34 (2H, d, J = 10.7 Hz, ArH), 8.11 (1H, d, J = 8.4 Hz, ArH), 7.87 (1H, d, J = 2.2 Hz, ArH), 7.74–7.63 (2H, m, ArH), 7.44 (1H, dd, J = 9.6, 2.1 Hz, ArH).

Table 1. *In vitro* antifungal activities of imidazo[1,2-a]pyridinyl-arylacrylonitriles against *Candida parapsilosis*

Compounds	Chemical Structures	MIC (μM)
3a		89.38
3b		42.27
3c		40.36
3d		85.11
3e		41.99
3f		38.49
3g		19.36
3h		39.79
3i		35.86
3j		39.79
Fluconazole		<2.55

^{13}C NMR (75 MHz, CDCl_3), δ , ppm: 140.83, 139.49, 131.15, 124.39, 117.91, 112.22, 107.55.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-(dimethylamino)phenyl)acrylonitrile (3g):

Yield – 76%. M. p. 196–200 °C. Brown lumpy powder. RF = 0.84 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ^1H NMR (300 MHz, CDCl_3), δ , ppm: 8.19 (2H, s, ArH), 7.91 (1H, s, ArH), 7.88 (1H, s, ArH), 7.85 (1H, s, ArH), 7.56 (1H, d, J = 9.6 Hz, ArH), 7.47–7.45 (1H, m, ArH), 7.44–7.41 (1H, m, ArH), 7.26 (1H, dd, J = 9.6, 1.9 Hz, ArH). ^{13}C NMR (75 MHz, CDCl_3), δ , ppm: 130.9, 129.5, 124.0, 117.6, 111.6.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(2-chlorophenyl)acrylonitrile (3h):

Yield – 69%. M. p. 214–218 °C. Beige lumpy powder. RF = 0.85 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ^1H NMR (300 MHz, DMSO-d_6), δ , ppm: 8.88–8.84 (1H, m, ArH), 8.40 (1H, s, ArH), 8.35 (1H, s, ArH), 8.13–8.07 (1H, m, ArH), 7.71 (1H, d, J = 9.7 Hz, ArH), 7.68–7.64 (1H, m, ArH), 7.58–7.51 (2H, m, ArH), 7.44 (1H, dd, J = 9.6, 2.2 Hz, ArH). ^{13}C NMR (75 MHz, DMSO-d_6), δ , ppm: 144.53, 141.89, 138.70, 135.27, 132.11, 131.55, 130.16, 129.33, 127.87, 127.32, 123.89, 118.16, 116.96, 111.84, 107.01.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(2,4-dichlorophenyl)acrylonitrile (3i):

Yield – 92%. M. p. 203–207 °C. Beige crystalline powder. RF = 0.79 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ^1H NMR (300 MHz, DMSO-d_6), δ , ppm: 8.86 (1H, dd, J = 2.2, 0.9 Hz, ArH), 8.34 (2H, d, J = 10.7 Hz, ArH), 8.11 (1H, d, J = 8.4 Hz, ArH), 7.87 (1H, d, J = 2.2 Hz, ArH), 7.74–7.63 (2H, m, ArH), 7.44 (1H, dd, J = 9.6, 2.1 Hz, ArH). ^{13}C NMR (75 MHz, DMSO-d_6), δ , ppm: 144.28, 140.44, 136.41, 136.14, 135.19, 131.09, 130.79, 130.08, 128.50, 128.28, 125.85, 120.19, 118.08, 116.78, 113.45, 108.52.

(Z)-2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-3-(4-chlorophenyl)acrylonitrile (3j):

Yield – 79%. M. p. 196–200 °C. Brown powder. RF = 0.84 cm (Mobile phase: Ethyl Acetate / Hexane, 70:30). ^1H NMR (300 MHz, CDCl_3), δ , ppm: 8.19 (2H, s, ArH), 7.91 (1H, s, ArH), 7.88 (1H, s, ArH), 7.85 (1H, s, ArH), 7.56 (1H, d, J = 9.6 Hz, ArH), 7.47–7.45 (1H, m, ArH), 7.44–7.41 (1H, m, ArH), 7.26 (1H, dd, J = 9.6, 1.9 Hz, ArH). ^{13}C NMR (75 MHz, CDCl_3), δ , ppm: 130.88, 129.50, 124.00, 117.59, 111.61.

The value of this coupling constant indicates that the imidazopyridinyl-acrylonitrile derivatives have a cis or (Z) configuration (Sissouma et al., 2011).

3.1.2 Antifungal activity

The antifungal activity of a series of imidazo[1,2-a]pyridinyl-arylacrylonitrile derivatives was evaluated in vitro against *Candida parapsilosis* by determining minimum inhibitory concentrations (MICs), expressed in μM . The compounds, differing in the nature of the substituent on the aromatic ring (Ar) of the arylacrylonitrile unit, exhibited significant variations in efficacy (Table 1).

3.2 Discussion

Following antifungal evaluations against *Candida parapsilosis*, all the molecules tested exhibited anticandidal activity ranging from 19.36 to 89.38 μM . Fluconazole, the reference substance, showed remarkable antifungal activity of less than 2.55 μM . Analysis of structure-activity relationship trends shows that:

3.2.1 Effect of the unsubstituted group

The reference compound (3a, Ar = H) exhibited limited activity (MIC = 89.38 μM), serving as a comparative basis.

3.2.2 Effects of different substitutions and parameter modifications

Influence of halogens: Halogenated substituents moderately enhanced activity. Monochlorinated derivatives in the ortho (3h, MIC = 39.79 μM) or para (3j) positions show similar efficacy (2.2 x greater than non-substituted derivative 3a), while the disubstituted 2,4-Cl (3i, MIC = 35.86 μM) suggests an additive effect. Fluorine derivative (3e, MIC = 41.99 μM) is slightly less active.

Role of electron donors: Hydroxy (3b, MIC = 42.27 μM) and methoxy (3c, MIC = 40.36 μM) derivatives provide only marginal improvement, while methyl (3d, MIC = 85.11 μM) remains less effective, reflecting the importance of polarizability.

Impact of electron acceptors: Nitro (3f, MIC = 38.49 μM) confers activity comparable to 4-Cl (3j), highlighting the benefits of electron-withdrawing substituents.

Contribution of tertiary amines: The dimethylamino group (3g, MIC = 19.36 μM) is distinguished by increased efficacy (4.6 times higher than 3a), likely due to better solubility,

membrane penetration, and affinity for fungal targets.

Structural modulation of the aryl ring drastically influences antifungal activity:

Polarizable groups like $(N(CH_3)_2)$ (3g) or electron-withdrawing substituents like halogens or NO_2 , significantly improve efficacy, while neutral (CH_3) or weakly donating (OCH_3) groups prove to be of little use. These results highlight the potential of halogenated and amine derivatives for the development of antifungal agents targeting *C. parapsilosis*, although their activity remains lower than that of fluconazole ($MIC < 2.55 \mu M$) used as reference drug.

4. CONCLUSION

This work is part of the search for new antifungal molecules. This is a preliminary work of pharmacochimistry whose aim is to propose molecules with a new chemical profile, with strong anticandidosis potential capable of circumventing the phenomena of drug resistance observed with most antifungal drugs. To do this, we designed, following the pharmacochimical concepts of molecular hybridization, molecules with a chemical profile of the type (6-chloroimidazo[1,2-a]pyridinyl)-3-phenylacrylonitriles. The synthesis of the expected imidazopyridine derivatives was carried out by condensation in a basic medium of imidazopyridines acetonitrile and aldehyde derivatives following the Knoevenagel method.

Structure-activity relationship studies have allowed us to establish certain hypotheses. Halogen substituents, particularly chlorine in ortho or di-substituted (2,4-Cl) positions, moderately improved antifungal activity compared to the unsubstituted parent compound. Electron-donating groups such as methoxy or hydroxyl had negligible impact, while methyl substitution (4- CH_3) led to poor activity. In contrast, electron-withdrawing groups like nitro (4- NO_2) and especially the strongly polarizable dimethylamino group (4- $N(CH_3)_2$) resulted in substantial activity enhancement, the latter exhibiting the best performance with a MIC of $19.36 \mu M$. Given that this preliminary study confirmed the antifungal potential of 6-chlorinated imidazopyridinyl acrylonitrile derivatives, such an evaluation of antifungal activity merits extension to other fungal species such as *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, and *Aspergillus*, which are also priority organisms according to the WHO.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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