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Synthesis Of New Imidazo [1,2-A] Pyridinyl-Chalcone Derivatives With Various Substitutions And Potentially Active Against Candida Krusei.

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Abstract

Imidazo[1,2-a]pyridinyl-chalcones represent a diverse chemical class that is found in the composition of many drugs. Their importance is all the greater because, in addition to being a source of investigation for the search for potential chemical compounds with anti-infective activity due to their structural similarity to natural flavonoids or chalcones, they contribute to the development of numerous drugs with various biological activities. This study focused on the pharmacochemical investigation of new derivatives with a structure of 1-(2,6-dimethylimidazo[1,2-a]pyridin-3-yl)-3-phenylprop-2-en-1-one, which were evaluated in-vitro for their antifungal activity. The results from these evaluations made it possible, on the one hand, to establish the structure-activity relationships of the synthesized molecules and, on the other hand, to demonstrate their antifungal activities through comparisons made between their Minimum Inhibitory Concentrations (MIC) and that of fluconazole or itraconazole identified as reference products. Thus, 9 compounds, derivatives of (E)-1-(2,6-dimethylimidazo[1,2-a]pyridin-3-yl)-3-phenylprop-2-en-1-one, showed MIC ranging from 19.6 µM to 47 µM with excellent antifungal activities against Candida krusei.

Keywords:*1-(2,6-dimethylimidazo[1,2-a]pyridin-3-yl)-3-phenylprop-2-en-1-one, antifungal, fluconazole, itraconazole, Candida krusei, Minimum Inhibitory Concentration*

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I. Introduction

The synthesis of new compounds of the imidazo[1,2-*a*]pyridinyl-chalcone type with various substitutions and their structural analogues plays a crucial role in the development of new drugs with diverse biological activities (1,2,3). In sub-Saharan Africa, despite the efforts and resources made available to successfully implement various health policies, such as the targeted free initiative for certain medications (4,5), access to effective drug therapy remains a real challenge for vulnerable populations (6,7).

Also, the resurgence of the HIV epidemic (8,9,10) has contributed to the increase of certain fungal infections attributed to non-albicans Candida (NAC) species such as *Candida krusei* (11). Indeed, *Candida krusei* is an opportunistic fungus, commensal to the digestive, respiratory and urogenital mucosa. It can be responsible for potentially fatal invasive candidiasis infections observed in some immunocompromised patients (12,13), as well as in patients with hematological diseases or those undergoing prolonged azole prophylaxis against fungal infections(14).

Furthermore, to address the shortage of certain drugs often considered ineffective or too costly, our research has focused on the synthesis of suitable therapeutic alternatives.

II. Methodology

The methodology was built around two main steps, the first of which involved the chemical synthesis of derivatives of 1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one, while the second focused on their *in vitro* evaluation against clinical fungal strains of *Candida krusei* using the standard microdilution method.

CHEMICAL SYNTHESIS

Synthesis Strategy

The chemical synthesis strategy implemented allowed the development of chemical derivatives of 1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one involving various condensation reactions (15). Indeed, the first condensation reaction occurs between 2-amino-5-methylpyridine and 3-chloropentan-2,4-dione in an ethanolic medium and under heat with stirring, resulting in the chemical synthesis of 2,6-dimethyl-3-acetyl-imidazo[1,2-*a*]pyridine.(15). The second condensation is carried out with the previously obtained product, namely 2,6-dimethyl-3-acetyl-imidazo[1,2-*a*]pyridine, in the presence of a benzaldehyde derivative in a basic medium to yield 1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one (Scheme 1) (16).

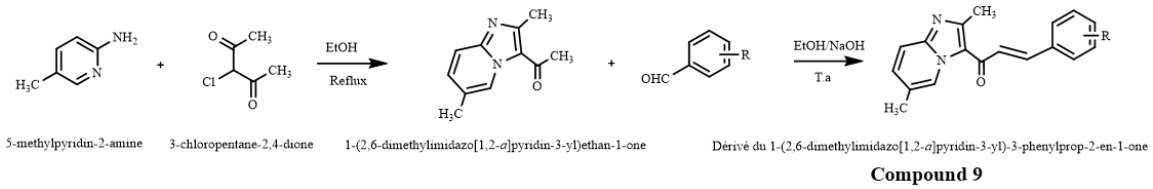
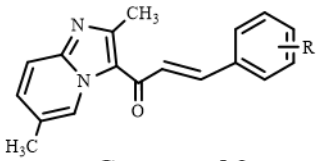


Figure 1 : Overall synthesis diagram

Synthesized Products

The different condensation reactions involved allowed the synthesis of nine derivatives of 1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one (scheme 2)



9a H (47%)
9b 4-Cl (58,7%)
9c 3-Cl (62%)
9d 3-CH3 (67%)
9e 4-CH3 (53,5%)
9f 4-N(CH3)2 (56%)
9g 4-F (51,8%)
9h 2,4-diOCH3 (49,3%)
9i 2-OH (49,7%)

Figure 2 : Derivatives of 1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one

III. Biological Method

Principle

The general principle is to incubate a suspension of the fungus to be tested in the presence of a series of increasing concentrations of the antifungal according to a geometric progression with a ratio of 2 (Table 1) and to determine the minimum inhibitory concentration (MIC), which corresponds to the lowest concentration of the antifungal or the experimental synthetic molecule capable of partially inhibiting (for fungistatic antifungals) or completely inhibiting (for fungicidal antifungals) the growth of the fungus. These techniques are generally carried out on 96-well microtiter plates with a "U" shape (17).

Table I: Range of Dilution and Concentration

Range of dilution	Concentration (µg/ml)		Range of dilution	Concentration (µg/ml)
1	100		6	3.125
2	50		7	1.5625
3	25		8	0.78125
4	12.5		9	0.390625
5	6.25		10	0.1953125

Operating Mode

Preparation of Synthesized Chemical Extracts (Chalcones)

The stock solutions of the different synthetic chemical extracts are prepared individually with Dimethylsulfoxide (DMSO) to give a working solution S0 at a concentration of 1 mg/ml. This S0 solution is obtained by using 150 µl of the S1 suspension added to 1350 µl of DMSO.

The S1 suspension for each molecule to be tested is prepared by mixing 1 mg of the synthetic molecule with 1 ml of DMSO. Then, the S0 solution is diluted in the enrichment broth B0 to obtain an S2 solution at a concentration of 10 µg/ml.

Next, 100 µl of the S2 solution is placed in all the wells of the first column.

Additionally, 50 µl of the yeast-free culture broth, called B0, is distributed into all the wells except those in the first column and the last two columns to serve as a control.

Perform microdilution by taking 50 µl from the well of the previous column each time, starting with column 1, to fill the wells of the following columns while respecting the order and direction of dilution. Add 50 µl of broth/inoculum B3 to all wells and let the plates incubate at 30°C for 48 hours.

Preparation of the Inoculum

Candida and Aspergillus cultures are grown on Sabouraud-Chloramphenicol agar at 30°C for 48 hours. Pick 1 to 3 colonies and inoculate them into 50 ml of a Tryptone-soy enrichment broth called B0 for 12 hours at room temperature to form broth B1. Then take 10 ml of the enrichment broth B1 and add it to 50 ml of a new Tryptone-Soy broth, creating broth B2, which should be kept under agitation at room temperature for 6 hours.

For the tests, 5 ml of broth B2 should be added to 50 ml of a new B0 broth to dilute it and obtain an inoculum B3 containing about a hundred fungal cells per milliliter, counted using a Malassez cell.

Malassez cells are devices used to quantify the number of cells in suspension in a solution, allowing for precise cell counting.The reading of the MIC is done after adding 40 µl of an aqueous solution of tetrazolium salt (MTT) to be evenly distributed in each well 2 hours beforehand. Aqueous MTT solution = 25 mg of MTT + 10 ml of sterile distilled water.

IV. Results

The analysis of the therapeutic effectiveness of the evaluated molecules was determined based on the MIC value of fluconazole, identified as the reference molecule.

Table 2: MIC Results of the Evaluated Molecules on *Candida krusei*

Molecules to be tested	MIC(µl/ml)	MIC(µg/ml)
9a	45.2	12.5
9b	40.2	12.5
9c	40.2	12.5
9d	43	12.5
9e	43	12.5
9f	19.6	12.5
9g	42.5	12.5
9h	37.2	12.5
9i	47	12.5
Fluconazole	**40.8**	**12.5**

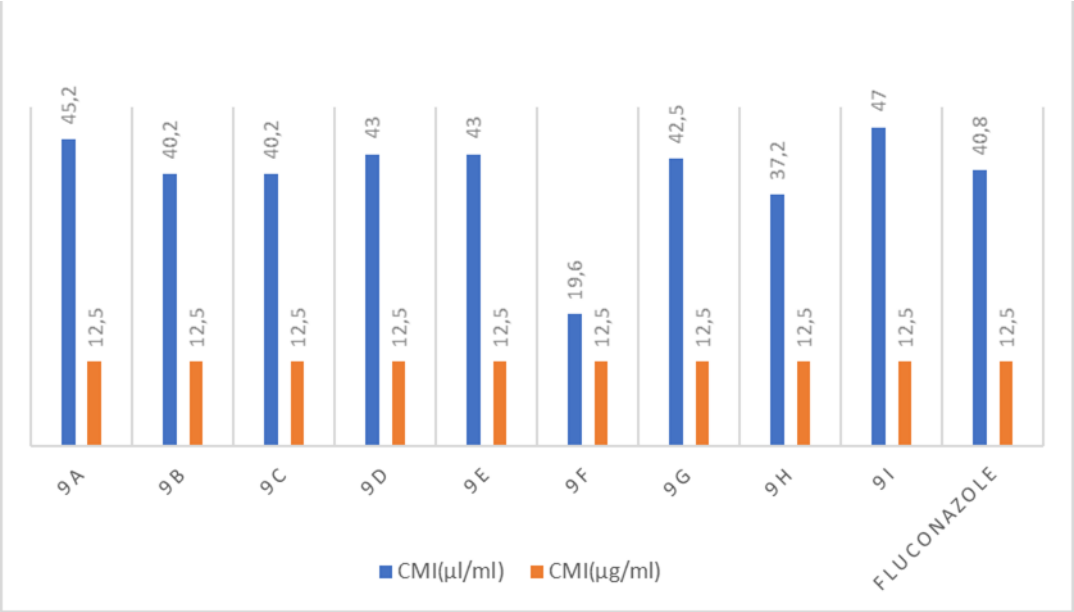


Figure 3: MIC Comparison Diagram

V. Discussion

The molecules evaluated *in vitro* on *Candida krusei* fungal strains allowed for the identification of different therapeutic activities depending on their fungal sensitivity. Indeed, compounds 9a, 9d, 9e, 9g, and 9i, carrying respectively hydrogen, 3-methyl, 4-methyl, 4-fluoro, and 2-hydroxy groups on the benzene ring of the phenyl-propenone chain, showed relative fungal sensitivity with MIC values statistically close to the reference molecule, which is 40.8 µM. Meanwhile, molecules 9b, 9c, and 9h, carrying 4-chloro, 3-chloro, and 4-dimethylamino groups, stood out with MIC thresholds lower than that of fluconazole, indicating greater fungal sensitivity than fluconazole and consequently good antifungal activity against *Candida krusei.*

Moreover, molecule 9f, whose MIC threshold value is half that of fluconazole, demonstrated very high sensitivity, resulting in excellent antifungal performance.

The evaluation of the antifungal activities of the synthesized molecules against the species *Candida krusei* showed that the introduction of functional groups on the benzene homocycle of the phenyl-prop-2-en-1-one group was beneficial for developing antifungal activities equal to or greater than those of fluconazole.

VI. Conclusion

The pharmacochemical method for designing new drug candidates has led to the development of ten molecules with good Minimum Inhibitory Concentrations comparable to that of fluconazole, correlated with excellent antifungal activities. Favorable structural elements

Analyses Spectroscopiques

Synthèse Générale des Dérives du (E)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)-3-phénylprop-2-èn-1-one

Mode Opératoire Général

1-acetyl-2,6-dimethyl-imidazo[1,2-*a*]pyridin (1 eq; 300 mg; 2 mmol) was dissolved in 10 ml of ethanol under magnetic stirring. To this mixture, a 20% sodium hydroxide solution and a benzaldehyde derivative (1.5 eq; 0.002 mol) were added. The reaction was allowed to stir for 24 hours. Subsequently, the obtained product

was treated with dilute hydrochloric acid, filtered, and then dried at room temperature. The yields obtained are related to the nature of the substituents present on the benzaldehyde.

(E)-1-(2,6-dimethyl-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one 9a

Analysis

RMN 1H (300 MHz, DMSO) δ 9,70 (s, J = 2,1 Hz, 1H) ; 7,89 (d, J = 13,4 Hz, 1H) ; 7,75-7,84 (m, 4H) ; 7,70 (dd,1H) ;7,65 (d,1H) ; 7,53 (d, J = 13,4 Hz, 1H) , ; 7,45 (d,1H); 2,53 (s, 3H) ; 2,31 (s, 3H)

RMN 13C (75 MHz, DMSO) δ 172, 14 ; 156,45 ; 155,53 ; 141,40 ; 138, 37 ; 134,46 ; 134,74 ; 130,48 ; 130,50 ; 128,83 ; 127,19 ; 126,35 ; 125,92 ; 123,54 ; 119,20 ; 25,54 ; 22, 63 ; 14,94.

(E)-3-(4-chlorophényl)-1-(2,6-diméthylimidazo[1,2-a]pyridin-3-yl)prop-2-èn-1-one 9b

Analysis

RMN 1H (300 MHz, DMSO) δ 9,76 (s, J = 2,2 Hz, 1H) ; 7,93 (d, J = 13,6 Hz, 1H) ; 7,70-7,79 (m, 4H) ; 7,84 (d,1H) ; 7,63 (d, J = 13,6 Hz, 1H) , 7,53 (d,1H) ; 2,83 (s, 3H) ; 2,51 (s, 3H)

RMN 13C (75 MHz, DMSO) δ 176, 14 ; 154,45 ; 153,5 ; 140,40 ; 139, 32 ; 133,46 ; 130,74 ; 130,18 ; 130,00 ; 128,03 ; 127,09 ; 126,31 ; 125,98 ; 121,54 ; 117,20 ; 24,54 ; 22, 63 ; 17,94.

(E)-3-(3-chlorophényl)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)prop-2-èn-1-one 9c

Analysis

RMN ^{1}H (300 MHz, DMSO) δ 9,74 (s, *J = 2,1 Hz*, 1H) ; 7,93 (d, *J = 13,6 Hz*, 1H) ; 7,70-7,79 (m, 4H) ; 7,84 (d,1H) ; 7,63 (d, *J = 13,6 Hz*, 1H) , 7,53 (d,1H) ; 2,83 (s, 3H) ; 2,51 (s, 3H)

RMN ^{13}C (75 MHz, DMSO) δ 176, 14 ; 154,45 ; 153,5 ; 140,40 ; 139, 32 ; 133,46 ; 130,74 ; 130,18 ; 130,00 ; 128,03 ; 127,09 ; 126,31 ; 125,98 ; 121,54 ; 117,20 ; 24,54 ; 22, 63 ; 17,94.

(E)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)-3-(m-tolyl)prop-2-èn-1-one 9d

Analysis

RMN ^{1}H (300 MHz, DMSO) δ 9,75 (s, *J = 2,1 Hz*, 1H) ; 7,87 (d, *J = 14,4 Hz*, 1H), 7,62-7;78 (m, 5H) ; 7,56 (d, *J = 14,4 Hz,* 1H) ; 7,16 (s,1H) ; 2,81 (s, 3H) ; 2,37 (s, 3H) 2,18 (s, 3H)

RMN ^{13}C (75 MHz, DMSO) δ 182,43 ; 158,73 ; 155,26 ; 142,29 ; 140,41 ;139,75 ; 133,38 ; 131,22 ; 130,01 ; 129,02 ; 128,88 ; 125,97 ; 125,73 ; 124,54 ;123, 4 ; 117,18 ; 21,16 ; 19, 48 ; 18,45.

(E)-1-(2,6-dimethylimidazo[1,2-a]pyridin-3-yl)-3-(p-tolyl)prop-2-en-1-one 9e

Analysis

RMN 1H (300 MHz, DMSO) δ 9,74 (s, J = 2,1 Hz, 1H) ; 7,93 (d, J = 13,4 Hz, 1H) ; 7,76-7,85 (m, 4H) ; 7,64 (d,1H) ; 7,53 (d, J = 13,4 Hz, 1H) ; 7,45 (d,1H) 7,45 (s,3H); 2,53 (s, 3H) ; 2,31 (s, 3H)

RMN 13C (75 MHz, DMSO) δ 175, 14 ; 157,45 ; 156,54 ; 142,40 ; 149, 37 ; 134,46 ; 134,75 ; 132,48 ; 130,50 ; 128,83 ; 127,19 ; 126,32 ; 124,32 ; 122,54 ; 118,20 ; 26,54 ; 23, 64 ; 15,94.

(E)-3-(4-(diméthylamino)phényl)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)prop-2-èn-1-one 9f

Analysis

RMN ^{1}H (DMSO-d6, δ ppm) : 9,60 (s, *J = 4,5 Hz*, 1H) ; 7,87 (d, *J = 16,3 Hz*, 1H) ; 7,52-6,69 (m, 6H) ; 7,48 (d, *J = 16,3 Hz*, 1H) ; 2,89-2,86 (s, 6H) ;2,85 (s, 3H) , 2,65 (s, 3H)

RMN ^{13}C (DMSO-d6, δ ppm) : 189,38 ; 177,83 ; 158,62 ; 155,65 ; 152,46 ; 143,45 ; 139,40 ; 133,71 ; 128,31 ; 125,37 ; 125,36 ; 124,84 ; 122,76 ; 121,30 ; 114,68 ; 37,20 ; 24,34 ; 18,10.

(E)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-fluorophényl)prop-2-èn-1-one 9g

Analysis

RMN ^{1}H (300 MHz, CDCl3) δ 9,89 (s, *J = 3,0 Hz*, 1H) ; 7,80 (d, *J = 15,7 Hz*, 1H) ; 6,6-7,51 (m,6H) ; 7,48 (d, *J = 15,7 Hz*, 1H) ; 2,90 (s,3H) ; 2,58 (s,3H).

RMN ^{13}C (75 MHz, CDCl3) δ 178,87 ; 157,42 ; 143,76 ; 137,25 ; 136,42 ; 128,22 ; 125,82 ; 118,75 ; 115,47 ; 98,33 ; 86,75 ; 78,52 ; 55,84 ; 53,75 ; 41,32 ; 18,53.

(E)-1-(2,6-dimethylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one 9h

Analysis

RMN ^{1}H (300 MHz, DMSO) δ 9,87 (s, *J = 2,1 Hz*, 1H) ; 7,92 (d, *J = 15,8 Hz*, 1H) ; 6,65-7,85 (m, 4H) ; 7,42 (s,1H) ;7,28 (d, *J = 15,8 Hz*, 1H) , 3,86-3,79 (s,6H) ; 2,80 (s, 3H) ; 2,63 (s, 3H) .

RMN ^{13}C (75 MHz, CDCl3) δ 184,18 ; 160,45 ; 157,4 ;154,67 ; 149,32 ; 144,33 ; 139,46 ; 129,32 ; 126,32 ; 124,69 ; 118,45 ; 116,87 ; 111,37 ; 110,42 ; 97,73 ; 58,48 ; 55, 65 ; 33,70. 19,56 ; 18,36.

(E)-1-(2,6-diméthylimidazo[1,2-*a*]pyridin-3-yl)-3-(2-hydroxyphényl)prop-2-èn-1-one 9i

Analysis

RMN ^{1}H (300 MHz, CDCl3) δ 13,19 (s, 1H) ; 9,52 (s, 1H) ; 8,47 (d, *J = 14,5 Hz*, 1H) ; 7,12-7,87 (m, 4H) ; 7,45 (d, *J = 8.3Hz*; 1H) ; 6,85 (d, *J = 7.9Hz*; 1H) ; 6,72 (d, *J = 14,5 Hz*, 1H) ; 2,65 (s, 3H) ; 2;48 (s, 3H).

RMN ^{13}C (75 MHz, CDCl3) δ 166,29 ; 162,78 ; 158,98 ; 152,82 ; 139,16 ; 137,25 ; 135,72 ; 132,42 ; 127,15 ; 124,37 ; 119,79 ; 117,35 ; 78,72 ; 76,53 ; 53,72; 42,38. 23,42 ; 16,87.

References

[1]. Nadia A. A. Elkanzi*Hajer Hrichiruba A. Alolayanwassila Derafafatin M. Zahourania B. Bakr. Synthesis Of Chalcones Derivatives And Their Biological Activities: A Review. ACS Omega 2022, 7, 32, 27769–27786.Https://Doi.Org/10.1021/Acsomega.2c01779

[2]. Henry, Elecia J.; Bird, Susan J.; Gowland, Pauline; Collins, Michael; Cassella, John P. Ferrocenyl Chalcone Derivatives As Possible Antimicrobial Agents. Journal Of Antibiotics (2020), 73 (5), 299-308CODEN: JANTAJ; ISSN:0021-8820

[3]. Benouda, H.;Bouchal, B.;Challioui, A.;Oulmidi, A.; Harit, T.;Malek, F.; Riahi, A.;Bellaoui, M.; Bouammali, B. Synthesis Of A Series Of Chalcones And Related Flavones And Evaluation Of Their Antibacterial And Antifungal Activities. Letters In Drug Design & Discovery.2018,16 (1),93–100,DOI: 10.2174/1570180815666180404130430

[4]. Valéry Ridde, Jean-Pierre Olivier De Sardan.Étudier Les Politiques Publiques Et Les Politiques De Santé En Afrique De l'Ouest.Afrique Contemporaine. 2012/3 N° 243, Pages 98 À 99

[5]. Mama Hamimida.Abdelmalik Hmaidi. Économie Politique De La Santé En Afrique : Dynamiques, Défis Et Innovations.Vigie Afriques | Volume 8, Numéro 2, Juillet 2025

[6]. Valerie Gateaux, Jean-Michel Heitz. L'accès Aux Médicaments : Un Défi Pour L'industrie Pharmaceutique.ÉDITIONS Humanisme Et Entreprise.DANS Varia 2008/1, PAGES 13 À 28.ISSN 0018-7372.DOI 10.3917/Hume.286.0013

[7]. Florentia Kaguelidou , Maria Ouèdraogo, Jean-Marc Treluyer Et Al. Développement Des Médicaments En Pédiatrie : Défis Existants Et Recommandations.Volume 78, Issue 1, 2023, Pages 95-104.Https://Doi.Org/10.1016/J.Therap.2022.12.002

[8]. Fanny Mach, Hélène Marchandin, Florence Bichon, Les Infections Sexuellement Transmissibles, Une Recrudescence Préoccupante, Actualités Pharmaceutiques,Volume 60, Issue 608, Supplement,2021,Pages 8-12, Https://Doi.Org/10.1016/J.Actpha.2021.06.020.

[9]. Sonia Raffe, Suneeta Soni, Diagnostic Tests For Sexually Transmitted Infections,Medicine, Volume 46, Issue 5,2018, Pages 277-282, Https://Doi.Org/10.1016/J.Mpmed.2018.02.008.

[10]. Meriem Bel Houari, Imane Zhim, Nadia Bouhlala, Abdnbi Amezouar, Waffae E Ennefah, Jamal Lmsaouri. Prise En Charge Médicamenteuse Des Principales Mycoses Opportunistes Chez Le Patient Infectés Par Le VIH. Cahiers Santé Médecine Thérapeutique. 2024;33(3):147-150. Doi:10.1684/Sanmt.2024.258

[11]. Zheng, T., Ji, L., Chen, Y., Cao, C., Bing, J., Hu, T., … Huang, G. (2024). Biology And Genetic Diversity Of Candida Krusei Isolates From Fermented Vegetables And Clinical Samples In China. Virulence, 15(1). Https://Doi.Org/10.1080/21505594.2024.2411543

[12]. Jamiu AT, Albertyn J, Sebolai OM, Pohl CH. Update On Candida Krusei, A Potential Multidrug-Resistant Pathogen. Med Mycol. 2021 Jan 4;59(1):14-30. Doi: 10.1093/Mmy/Myaa031. PMID: 32400853.

[13]. Abbas J, Bodey GP, Hanna HA Et Al. Candida Krusei Fungemia. An Escalating Serious Infection In Immunocompromised Patients. Arch Intern Med. 2000; 160(17): 2659–2664

[14]. Thi Anh Nguyen, Hannah Yejin Kim, Sophie Et Al., Pichia Kudriavzevii (Candida Krusei): A Systematic Review To Inform The World Health Organisation Priority List Of Fungal Pathogens, Medical Mycology, Volume 62, Issue 6, June 2024, Myad132, Https://Doi.Org/10.1093/Mmy/Myad132

[15]. J. G. Lombardino, Preparation And New Reactions Of Imidazo[1,2-A]Pyridines, J. Org. Chem., 1965, 30, 2403-2407.

[16]. Rahman AF, Ali R, Jahng Y, Kadi AA. A Facile Solvent Free Claisen-Schmidt Reaction: Synthesis Of A,A'-Bis-(Substituted-Benzylidene)Cycloalkanones And A,A'-Bis-(Substituted-Alkylidene)Cycloalkanones. Molecules. 2012 Jan 9;17(1):571-83. Doi: 10.3390/Molecules17010571. PMID: 22231494; PMCID: PMC6269007.

[17]. CLSI. 2004. Method For Antifungal Disk Diffusion Susceptibility Testing Of Yeasts: Approved Guideline. Document M-44A. Clinical And Laboratory Standards Institute, Wayne, Pa. Available On URL Www.Nccls.Org 9.