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Design and structure-activity relationships anticandidosic of diazaheteroaryl functionalized by Michaël acceptors

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Abstract

Benzimidazole and imidazopyridine heterocycles associated with Michaël acceptors have shown strong anticandidosic potential in our previous work. After a decade of research, we have designed, synthesized and evaluated the anticandidosic activities of several new compounds with the structure benzimidazolyl-arylpropenone or benzimidazolyl-arylacrylonitriles or benzimidazolyl-arylcyanopropenone and imidazopyridinyl-arylpropenone. The evaluation of their antifungal activities by the bioautography method showed that these molecules possessed anticandidosic properties with MIQs ranging from 10 to 0.16 µg. These results also highlighted that the anticandidosic performance of our compounds was related to the nature of the Michaël acceptor and structural variations undertaken on the benzene homocycle. In this paper, we discuss the pharmacochemical design, the chemical synthesis and especially the structure-activity relationship studies of diaza-heteroaryls functionalized by a Michaël acceptor of the arylpropenone or arylacrylonitrile or arylcyanopropenone type.

***Keywords*:** Michaël acceptors, diaza-heteroaryls, benzimidazole, imidazopyridine, anticandidosic.

1. Introduction

Candidiasis is a fungal infection caused by the genus *Candida*, whose main species is *Candidaalbicans* [**1**]. *Candida albicans* is part of the normal human flora and can become pathogenic in the presence of certain factors such as HIV/AIDS, diabetes, cancer and many others [**2**]. Depending on their location, we distinguish between superficial candidiasis, the most common of which is mucosal candidiasis, and deep or systemic candidiasis, which are the most serious forms of the disease [**3**]. Superficial candidiasis is recurrent in immunocompromised patients such as those living with HIV/AIDS. In these patients, fungi cause oropharyngeal candidiasis, which leads to swallowing difficulties, malnutrition and non-compliance with treatment, which can lead to fatal therapeutic failures [**4**]. As for systemic or even invasive candidiasis, these are the most serious forms of the disease and are constantly increasing due to immunosuppressive therapies, certain surgical procedures and certain diseases that reduce the body's natural defenses (cancer, Covid-19) [**5,6**]. In addition, new non-*albicans* species are emerging, often refractory to current a antifungal drug, which increases the negative impact of candidiasis on the duration and cost of hospitalization of patients, as well as on the morbidity and mortality rate [**7**]. It is in this context that our research team has been working for several years on the development of diaza-heteroaryl compounds functionalized by Michaël acceptors as potential new anticandidosic agents.

2. Materials and methods

2.1. Design of diaza-heteroaryls functionalized by Michaël acceptors

In the context of fungal resistance to most antifungal drugs, the development of new molecules likely to be more effective remains an essential weapon. It is in this context that our research team has been working for several years on the design of new hybrid antifungal molecules. These hybrid molecules have been designed by judiciously associating diaza-heteroaryls (benzimidazole, imidazopyridine) with Michaël acceptors of the arylpropenone,

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arylacrylonitrile and arylcyanopropenone type. Thus, benzimidazolyl-arylpropenones were obtained by docking the para chlorobenzyl benzimidazole of Chlormidazole to the phenylpropenone functional chain of chalcones (**Figure 1**). This association is justified by the fact that *para* chlorobenzyl benzimidazole is the heterocyclic carrier of Chlormidazole, the first fully synthetic antifungal discovered in 1944 by Woolley [**8**]. In addition, the benzimidazole heterocycle is favorable for the induction of various anti-infective activities [**9**-**13**]. As for the phenylpropenone chain, it is responsible for the induction of numerous biological activities of chalcones, in particular antimalarial, antibacterial, antifungal and antiviral. In fact, this functional linkage carried by an aryl group, would be at the origin of the inhibition by complexation of certain microbial and cancerous enzymes with thiol function [**14**].

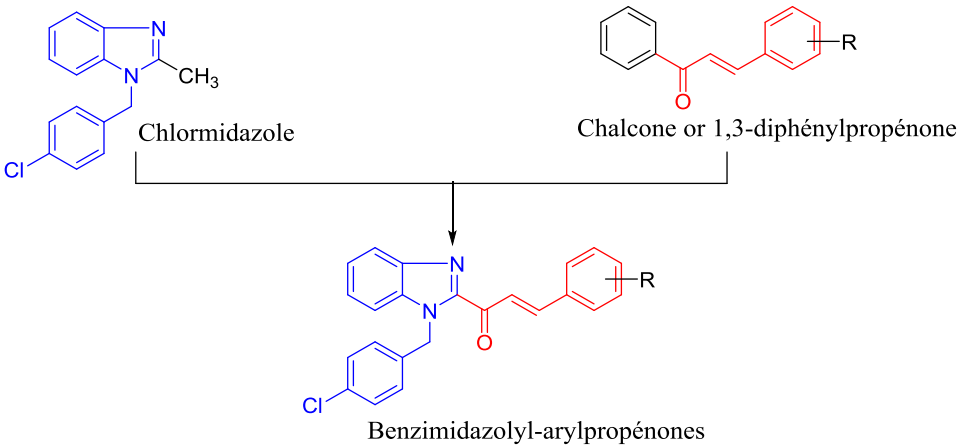


Figure 1 : Design of benzimidazolyl-arylpropenones

In addition, different structural variations have been undertaken around benzimidazolyl-arylpropenones in order to obtain structural analogues also possessing antifungal activities. These modifications allowed the design of benzimidazolyl-arylacrylonitriles (**Figure 2**) with antifungal activity by applying the concept of bioisostery of functional groups [**15**]. Indeed, the arylpropenone linkage of carbonyl α,β-ethylenic benzimidazolyl-arylpropenones was replaced by its nitrile α,β-ethylenic isostere arylacrylonitrile. Furthermore, arylacrylonitrile like arylpropenone behaves as a Michaël acceptor inhibiting certain biological targets with thiol functions [**14**, **16**]. Another chemical modification has led to the design of benzimidazolyl arylcyanopropenones (**Figure 2**) with antifungal targets. These could be considered as resulting from the structural combination of benzimidazolyl-arylacrylonitriles and benzimidazolyl-arylpropenones with the aim of bringing together in a single chemical profile, the propenone and acrylonitrile functional groups. Finally, the last modification consisted in replacing the benzimidazole by another diazotized heterocycle of imidazopyridine type. This choice was motivated by the fact that imidazopyridine is an isostere of benzimidazole following the internalization of the pyrrolic nitrogen of the latter into pyridine nitrogen. Moreover, this heterocycle is primarily a diazotized ring resulting from the docking of pyridine and imidazole. The imidazopyridinyl-arylpropenones (**Figure 2**) could also have anti-infectious properties, in particular antifungal properties like imidazole [**17**,**18**].

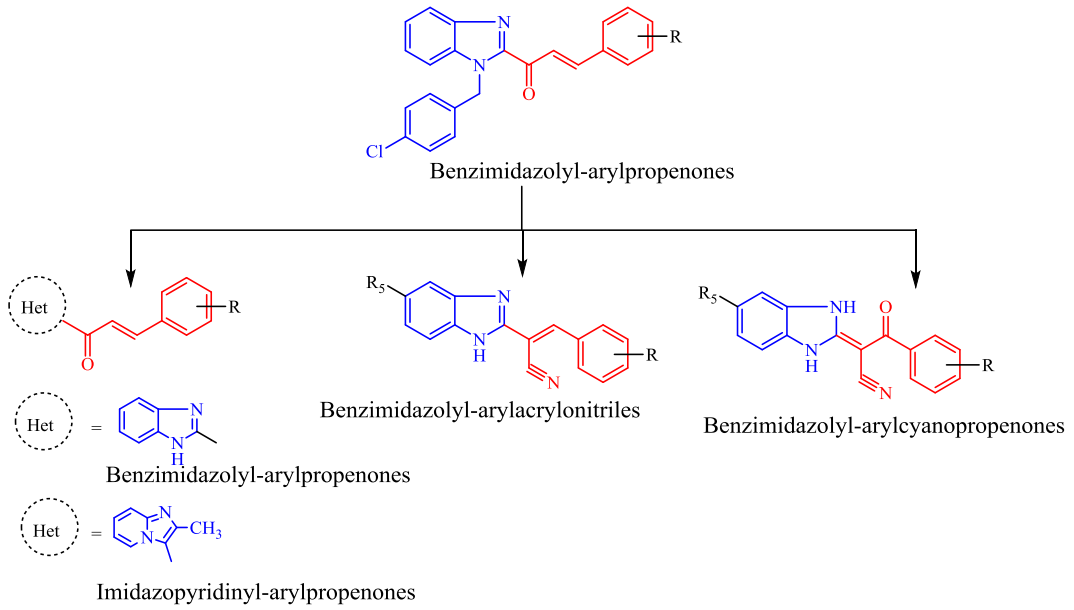


Figure 2 : Design of benzimidazolyl-arylpropenones and benzimidazolyl-arylacrylonitriles, benzimidazolyl-arylcyanopropenones and imidazopyridinyl-arylpropenones

2.2. Experimental

2.2.1. Chemical synthesis

All the obtained diaza-heteroaryl derivatives were characterized by the usual spectral methods. Nuclear Magnetic Resonance (NMR) spectra of ^{1}H proton (300MHz) and ^{13}C carbon (75 MHz) were recorded on a BrückerAvance 300 apparatus. Tetramethylsilane (TMS) is used as a reference for shifts expressed in ppm. Mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI (electrospray/quadrupole ionization) mode or an HP 5889A quadrupolar spectrometer in electron impact (EI). Melting points (FPs) were determined using a Kofler bench and are uncorrected. Thin layer chromatography (TLC) was performed on Macherey-Nagel Sil G/UV254 silica plates or on Macherey-Nagel ALOX N/UV254 alumina. The stains of the different derivatives were revealed by light at 254 nm or by iodine. Solvents and reagents including the ones from Acros Organics (France) or from Aldrich (France). Reference drugs such as Chlormidazole, Fluconazole and Ketoconazole were obtained from Sigma Chemical Co. (USA).

The synthesis of benzimidazolyl-arylpropenones (**scheme 1**) required the preliminary preparation of 2-hydroxyethyl-benzimidazole (**3**) by condensation between orthophenylenediamine (**1**) and lactic acid (**2**) according to the Phillips method [**19**]. The 2-hydroxyethyl-benzimidazole obtained was oxidized to 2-acetylbenzimidazole (**4**). The latter subsequently underwent an *N*-benzylation reaction using 4-chlorobenzyl chloride after the action of sodium hydride (NaH). The previously prepared 2-acetylbenzimidazole (**4**) and *N*-(4-chlorobenzyl) 2-acetylbenzimidazole (**5**) were engaged in a Claisen-Schmidt type condensation reaction in basic medium to lead to benzimidazolyl-arylpropenones [**20**, **21**].

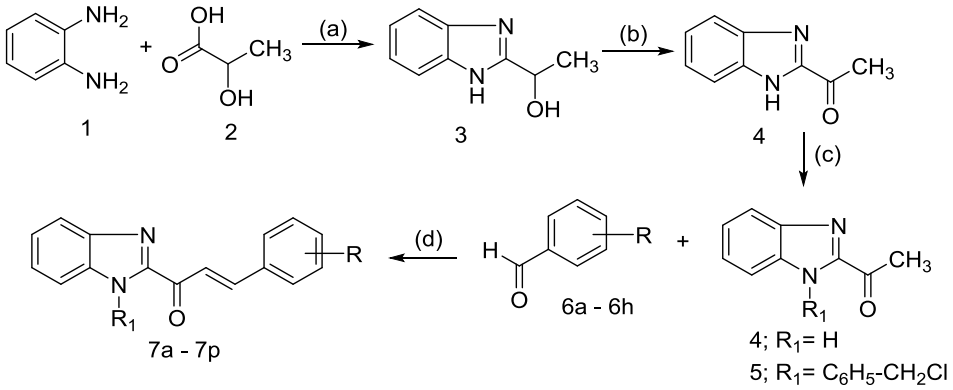
Synthesis of 2-acetylbenzimidazole (4)

To a flask containing orthophenylenediamine (4.8 g; 42 mmol) are added 50 mL of a 4N hydrochloric acid solution and lactic acid (4.5 mL; 60 mmol). The solution is heated at reflux for 45 min. The cooled reaction mixture is then neutralized with ammonia. The precipitate formed is filtered, washed with water and recrystallized with the same solvent to give 5.94 g of 2-hydroxyethylbenzimidazole. Subsequently, 3.5 g of the 2-hydroxyethylbenzimidazole (22 mmol) is dissolved in 30 mL acetic acid and 10 mL of an aqueous solution containing 3 g potassium dichromate (11 mmol) is added. The mixture is heated under reflux for 45 min and then cooled by an ice bath. After cold neutralization with ammonia, the precipitate is filtered and taken up with chloroform. The solvent is evaporated and the residue is purified by chromatography on silica gel (elution: DCM/AcOEt: 95/5). The yield is 72%.

Synthesis of N-(4-chlorobenzyl) 2-acetylbenzimidazole (5)

In a bicol immersed in ice water (about 0°c), 1eq (31.25mmol) of 2-acetylbenzimidazole is dissolved in 25ml of DMF. After cooling, 1.1eq (34.38mmol) of sodium hydride are added in small portions and the mixture is left under stirring for one hour. Then to the

still cooled mixture, 1.1eq (34.38mmol) of benzyl chloride are added dropwise. After 20H of stirring at room temperature, the mixture is poured onto pulverized ice. The precipitate formed is filtered, dried and then recrystallized in a water/ethanol mixture (1:1). The yield is 78%. General procedure for the synthesis of benzimidazolyl-arylpropenones derivated. To a flask containing 40 mL of ethanolic soda solution (75 mmol) is added 2-acetylbenzimidazole or N-(4-chlorobenzyl)2-acetylbenzimidazole (10 mmol) and suitably selected arylaldehyde (10.1 mmol). The reaction mixture is stirred at room temperature for 3 to 5 h. Neutralization of the medium with a 30% acetic acid solution gives a precipitate which is filtered and dried. The physicochemical properties and spectral data of the intermediates 2-acetylbenzimidazole (4) and N-(4-chlorobenzyl)2-acetylbenzimidazole (5) have been given in our previous papers [**20** – **23**]. The spectral data of the characteristic chemical groups and the mass spectra of benzimidazolyl-arylpropenones(**7a-7p**) are compiled in **Table 1**



Scheme 1: Synthetic pathways for access to benzimidazolyl-arylpropenones (**7a-7p**). Conditions and reagents: (a): HCl 4N / NH_4OH; (b): $K_2Cr_2O_7$ /AcOH; (c) NaH / C_6H_5-CH_2Cl; (d) NaOH, EtOH

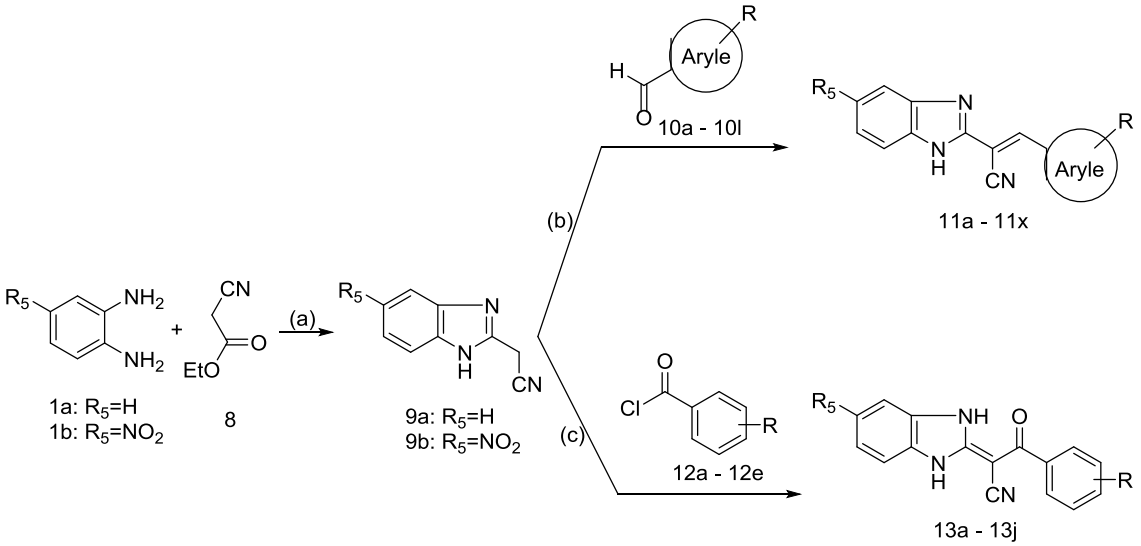
As for the benzimidazolyl-arylacrylonitriles (**Scheme 2**), their synthesis started with the condensation between suitably chosen orthophenylenediamine (**1a**;**1b**) and ethyl cyanoacetate (**8**) at reflux to lead to the corresponding 2-(1H-benzimidazol-2-yl) acetonitriles (**9a**; **9b**) [**22**]. Subsequently, the corresponding 2-(1H-benzimidazol-2-yl) acetonitriles (**9a**; **9b**) were condensed with aromatic aldehydes (**10a**-**10l**) in the presence of a few drops of piperidine at reflux in ethanol to lead to the expected benzimidazolyl-arylacrylonitriles [24]. On the other hand, reflux condensation of the corresponding 2-(1H-benzimidazol-2-yl) acetonitriles (**9a**; **9b**) with benzoyl chloride derivatives (**12a**-**12e**) in toluene afforded the benzimidazolyl-arylcyanopropenones [**24**]. The chemical synthesis route of benzimidazolyl-arylacrylonitriles and benzimidazolyl-arylcyanopropenones is summarized in **Scheme 2** below.

Synthesis of 2-(1H-benzimidazol-2-yl)acetonitriles

To a bicol containing 1eq of orthopenylphenediamine (2g; 185.2 mmol) or 5-nitro orthopenylphenediamine, 2eq (4.2g; 370.4 mmol) of ethyl cyanoacetate is added. The mixture is refluxed for 6 hours. After cooling, 150 mL of ether is added to the reaction mixture, the resulting precipitate is filtered and then recrystallized in water. Brown crystals of 2-(1H-benzimidazol-2-yl)acetonitrile (**9a**) and orange crystals of 2-(5-nitro-1H-benzimidazol-2-yl)acetonitrile (**9b**) are obtained in yields around 30% .

Synthesis of benzimidazolyl-arylacrylonitriles

In a bicol, 1 eq (6.37 mmol) of 2-(1H-benzimidazol-2-yl)acetonitrile or 5-niro 2-(1H-benzimidazol-2-yl)acetonitrile is dissolved in 10 mL of anhydrous ethanol. Five drops of piperidine are added, followed by 1.1 eq (7 mmol) of benzaldehyde derivatives. The reaction mixture is refluxed for 1h. After cooling, the precipitate obtained is filtered and air-dried. The products are purified by washing with reflux in hexane. Synthesis of benzimidazolyl-cyanoarylpropenone In a bicol, 1equivaqent of 2-(1H-benzimidazol-2-yl)acetonitrile (1g; 6.98 mmol) or 1equivalent of 5-niro 2-(1H-benzimidazol-2-yl)acetonitrile (1g; 5.31 mmol) is dissolved in 15 mL toluene. 1.1 equivalents of the benzoyl chloride derivative are added. The reaction mixture is refluxed for 4 h. After cooling, the resulting precipitate is filtered and air-dried. The products are purified by reflux washing in ethanol or by recrystallization. The spectral data of the characteristic chemical groups and the mass spectra of benzimidazolyl-cyanoarylpropenones (**13a-13j**) are compiled in **Table1.**..



Scheme 2: Synthetic pathways for access to benzimidazolyl-arylacrylonitriles (**11a**-**11x**) and benzimidazolyl-arylcyanopropenones (**13a** -**13j**). Conditions and reagents: (a): reflux; (b):pipéridine/ EtOH; (c): Toluène / reflux.

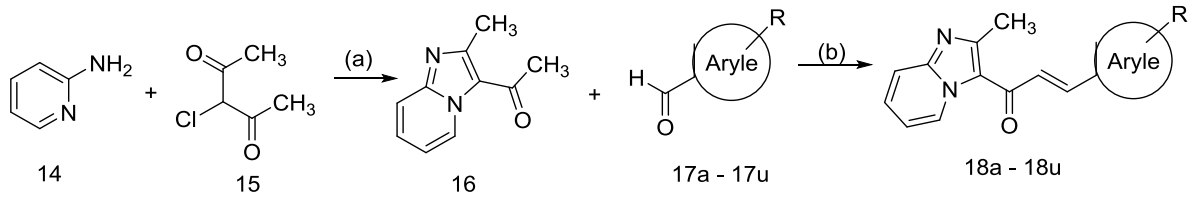
For the synthesis of imidazopyridinyl-arylpropenones (**Scheme 3**), 3-acetyl-2-methylimidazopyridine (**16**) was previously prepared by condensation between 2-animopyridine (**14**) and 3-chloro-pentan-2,4-dione (**15**) at reflux in ethanol followed by neutralization with ammonium hydroxide solution (NH_4OH). The previously prepared 3-acetyl-2-methylimidazopyridine (**16**) is subsequently engaged in a Claisen-Schmidt type basic condensation reaction with various substituted aromatic aldehydes (**17a**-**17u**) to lead to the expected imidazopyridinyl-arylpropenones [**25**, **26**].

Synthesis of 3-acetyl-2-methylimidazo[1,2-a]pyridine (16)

To a solution of 2-aminopyridine (4.8 g; 42 mmol) in absolute ethanol (50 mL) was added 1.05 equivalents of 3- chloro pentan-2,4-dione (14.4 g; 107 mmol). The reaction mixture was stirred under reflux for 6 hours. After evaporating the solvent under vacuum, 125 mL of water was added then neutralized with a saturated solution of sodium bicarbonate. The resulting solution was stored in a refrigerator for 5 hours. The precipitate obtained is filtered and recrystallized from water to afford 3-acetyl-2-methylimidazo[1,2-a]pyridine (16) as white solid.

Synthesis of imidazopyridinyl-arylpropénones (18a-18u)

To a stirred solution of 3-acetyl-2-methylimidazo[1,2-a]pyridine (1.5 g, 8.62 mmol) in an ethanolic solution of sodium hydroxide (64.6 mmol of NaOH in 40 mL of ethanol), was added the appropriate benzaldehyde (10.35 mmol, 1.2 mol equivalent). The mixture was kept under stirring at room temperature for 5 h. After neutralization with a CH_3COOH (30%), the resulting precipitate was dried. The corresponding solid products 18a-18u were further purified by recrystallization with a yield of 30 to 85%. The physicochemical properties and spectral data of the 3-acetyl-2-methylimidazo[1,2-a]pyridine intermediate (16), have been given in an earlier paper [**25**, **26**].The spectral data of the characteristic chemical groups and the mass spectra of imidazopyridinyl-arylpropénones (**18a**-**18u**)are compiled in **Table 1**.



Scheme 3: Synthetic pathways for access to imidazopyridinyl-arylpropénones (**18a**-**18u**). Conditions and reagents: (a): EtOH / NH_4OH; (b): NaOH, EtOH.

Table 1: ^{1}H, ^{13}C NMR of characteristic chemical groups and mass spectrometry of compounds

Compounds	^{1}H, ^{13}C NMR of characteristicchemical groups (DMSOd6, δ ppm) and mass spectrometry
7a	^{1}H:8.29(1H,d,J=15.8Hz,CH=CH);7.92(1H,d,J=15.8Hz,CH=CH);5.94(2H,s,CH2).13C:182.72(C=O);140.99(CH=CH);122.84(CH=CH);48.20(CH2). SM: 373([M]+,100). Column chromatography(eluent:hexane/dichloromethane:30/70).Yield=73%.MP=150-152°C
7b	^{1}H: 8.30(1H,d,J=15.8Hz,CH=CH);7.98(1H,d,J=15.8Hz, CH=CH);5,98(2H,s,CH_2). ^{13}C:182.83(C=O); 140.96(CH=CH); 122.03(CH=CH); 47.97(CH2). SM: 387([M] +, 100). Washing in hot hexane. Yield = 86%. MP = 172-174°C
7c	^{1}H: 8.30 (1H, d,J = 15.8 Hz,CH=CH);7.81 (1H,d, J = 15.8 Hz, CH=CH);5.96 (2H,s,CH_2). ^{13}C:182.01(C=O); 140.55(CH=CH); 122.12(CH=CH); 48.21(CH_2). SM: 389([M+H] +, 100). Washing in hot hexane. Yield = 79%. MP = 168-170°C
7d	^{1}H: 8.27 (1H, d,J = 15.8 Hz,CH=CH);7.79 (1H,d, J = 15.8 Hz,CH=CH);5.91 (2H,s,CH_2). ^{13}C:180.35(C=O); 140.55(CH=CH); 121.98(CH=CH); 47.55(CH_2). SM: 403([M+H] +, 100). Washing in hot hexane. Yield = 79%. MP = 168-170°C
7e	^{1}H: 8.29 (1H, d,J = 15.8 Hz,CH=CH);7.92 (1H,d, J = 15.8 Hz,CH=CH);5.95 (2H,s,CH_2). ^{13}C:182.72(C=O); 141.86(CH=CH); 123.01(CH=CH); 47.76(CH2). SM: 407([M] +, 80). Column chromatography(eluent:hexane/dichloromethane:50/50).Yield=40%.MP>260°C
7f	^{1}H: 8.28 (1H, d,J = 15.8 Hz,CH=CH);7.94 (1H,d, J = 15.8 Hz,CH=CH);5.98 (2H,s,CH2). ^{13}C:182.81 (C=O); 141.88 (CH=CH); 123.11 (CH=CH); 47.89(CH_2). SM: 451([M]+,80). Column chromatography(eluent:hexane/dichloromethane:50/50).Yield=40%.MP= 179-181°C
7g	^{1}H: 8.25 (1H, d,J = 15.8 Hz,CH=CH);7.86 (1H,d, J = 15.8 Hz,CH=CH);5.93 (2H,s,CH_2). ^{13}C:182.35(C=O); 136.55(CH=CH); 122.02(CH=CH); 48.25(CH_2). SM: 391([M+H] +,100). Column chromatography (eluent: hexane / dichloromethane: 30/70). Yield = 79%. MP = 168-170°C
7h	^{1}H:8.39(1H,d,J=15.8Hz,CH=CH);8.10-7.85(4H,m,CH=CH and HAr);5.94(2H,s,CH_2). ^{13}C:183.01(C=O); 136.58(CH=CH); 122.03(CH=CH); 48.27(CH_2). SM: 452([M]+,35). Recrystallization from toluene. Yield = 50%. MP= 150-152°C
7i	^{1}H: 8.28(1H, d, J=16Hz,CH=CH);8.15(1H,d,J=16Hz,CH=CH); 5.94 (2H,s,CH_2). ^{13}C:181. ^{13}(C=O); 143.97 (CH=CH); 121.69 (CH=CH). SM: 249 ([M+H] +, 100). Recrystallization from toluene. Yield = 54%. MP =216-218°C
7j	^{1}H:13.20(1H,s,NH);8.15(1H,d,J=15.6Hz, CH=CH);8.03(1H,d,J=15.6Hz,CH=CH). ^{13}C: 181.09(C=O); 149.02 (C=N); 143.30 (CH=CH);121.69 (CH=CH). SM: 263 ([M+H] +, 100). Recrystallization from ethanol. Yield= 66%.MP=201-203°C
7k	^{1}H:14(1H,s,NH);7.99(1H,d,J=15.6Hz, CH=CH);7.94(1H,d,J=15.6Hz,CH=CH). ^{13}C: 181.13(C=O); 149.60 (C=N); 145.16(CH=CH); 121.69(CH=CH). SM: 265 ([M+H] +, 100). Recrystallization from ethanol/toluene. Yield= 58%.MP=203-205°C
7l	^{1}H:13.54(1H,s,NH);8.30(1H,d,J=16Hz,CH=CH);8.12(1H,d,J = 16Hz,CH=CH). ^{13}C:181.23(C=O); 149.34 (C=N); 138.76(CH=CH); 121.49(CH=CH). SM: 279 ([M+H] +, 100). Recrystallization from toluene. Yield= 69%.MP=165-167°C
7m	^{1}H:8.01(1H,d,J=15Hz,CH=CH);7.96(1H,d,J=15Hz,CH=CH). ^{13}C:180.00(C=O);142.25 (CH=CH);122.01 (CH=CH). SM:283([M+H] +,100). Recrystallization from ethanol/toluene:1/4. Yield=47%. MP>260°C.
7n	^{1}H:14(1H,s,NH);8.01(1H,d,J=15Hz,CH=CH); 7.95 (1H, d, J = 15 Hz, CH=CH). ^{13}C:179.91(C=O);149.40(C=N);142.50 (CH=CH); 122.01 (CH=CH). SM: 328 ([M+H] +, 100). Recrystallization from toluene. Yield= 73 %.MP=228-230°C
7o	^{1}H: 8.01(1H, d, J=15.8Hz, CH=CH); 7.91(1H, d, J=15.8Hz, CH=CH). ^{13}C:180.80(C=O); 142.55 (CH=CH); 122.01 (CH=CH). SM: 267 ([M+H] +, 100). Recrystallization from toluene. Yield = 81%. MP =222-224°C
7p	^{1}H: 8.39(1H, d, J=15.9Hz, CH=CH); 8.10-7.85(2H, m, CH=CH and HAr). ^{13}C:183.01(C=O); 136.58 (CH=CH); 122.09(CH=CH).

	SM: 328([M+H] +, 100). Recrystallization from ethanol/toluene:1/1.Yield =45%.MP=208-210°C
11a	^{1}H:8.40 (1H,s,C=CH).^{13}C:145.14 (C=CH);116.04(C≡N);102.38 (C=CH).SM[EI, 70eV]:245([M]$^{+}$,39);244([M-H]$^{+}$,96). Washing in hot hexane.Yield=52%. MP =222-224°C
11b	^{1}H: 8.31(1H, s, C=CH). ^{13}C:145.35(C=CH); 116.35(C≡N); 101.11(C=CH).SM[IC, NH_3]:258([M-H]$^{+}$,100). Washing in hot hexane.Yield=85%.MP =228-230°C
11c	^{1}H:8.22(1H,s,C=CH).^{13}C: 145.40(C=CH);116.92(C≡N);97.57(C=CH).SM[IC, NH_3]:260([M-H]$^{+}$,100). Washing in hot hexane. Yield=78%.MP >260°C
11d	^{1}H:8.16(1H,s,C=CH).^{13}C: 145.48(C=CH);117.74(C≡N);93.53 (C=CH).SM[EI,70 eV]:287([M-H]$^{+}$,100). Washing in hot hexane. Yield=93%.MP >260°C
11e	^{1}H:8.31(1H,s,C=CH).^{13}C:145.04(C=CH);116.71(C≡N);98.92(C=CH). SM[IC, NH_3,m/z]:274([M-H]$^{+}$,100). Washing in hot hexane. Yield=70%.MP =240-241°C
11f	^{1}H:8.56(1H,s,C=CH).^{13}C: 141.11(C=CH);117.62 (C≡N);104.26(C=CH). SM[IC, NH_3]:305 ([M]$^{+}$,43);304([M-H]$^{+}$,100). Washing in hot hexane. Yield=67%.MP =242-244°C
11g	^{1}H:8.22(1H,s,C=CH).^{13}C: 142.26(C=CH);115.28(C≡N);106.7(C=CH). SM [EI, 70 eV]: 291 ([M+ 1]$^{+}$, 100). Washing in hot hexane. Yield= 50%. MP >260°C
11h	^{1}H:8.50(1H,s,C=CH).^{13}C: 145.23 (C=CH);119.43(C≡N);106.65(C=CH). SM[IC, NH_3]:279 ([M]$^{+}$,34);278([M-H]$^{+}$,100). Washing in hot hexane. Yield=88%.MP =250-252°C
11i	^{1}H:8.46(1H,s,C=CH).^{13}C: 139.96 (C=CH);115.19(C≡N);107.15(C=CH). SM[EI,70 eV]:313([M-H]$^{+}$,100). Washing in hot hexane. Yield=80%.MP =256-258°C
11J	^{1}H:8.35 (1H,s,C=CH).^{13}C:143.92 (C=CH);115.95(C≡N);102.99 (C=CH). SM[EI,70eV]:323([M-H]$^{+}$,100). Washing in hot hexane.Yield=70%.MP =250-252°C
11k	^{1}H:8.25 (1H,s,C=CH).^{13}C:141.90 (C=CH);115.12(C≡N);104.11 (C=CH). SM[EI,70eV]:236([M-H]$^{+}$,100). Washing in hot hexane.Yield=69%.MP =241-242°C
11l	^{1}H:8.33 (1H,s,C=CH).^{13}C:142.17 (C=CH);115.15(C≡N);103.99 (C=CH). SM[EI,70eV]:247([M-H]$^{+}$,100). Washing in hot hexane.Yield=62 %.MP =248-250°C
11m	^{1}H:8.36 (1H,s,C=CH). ^{13}C: 145.58 (C=CH);118.20(C≡N);106.16 (C=CH). SM[IC, NH_3]:291 ([M+1]$^{+}$,100). Washing in hot hexane. Yield=71%.MP >260°C
11n	^{1}H:8.45 (1H,s,C=CH). ^{13}C: 145.58 (C=CH); 118.20(C≡N); 106.16 (C=CH). SM[IC, NH_3]:305 ([M+1]$^{+}$,100). Washing in hot hexane. Yield=66%.MP >260°C
11o	^{1}H:8.28 (1H,s,C=CH). ^{13}C:143.64(C=CH);118.51(C≡N);100.11 (C=CH). SM[IE,70 eV]:306([M]$^{+}$,25);305 ([M-H]$^{+}$,100). Washing in hot hexane.Yield=59%.MP >260°C
11p	^{1}H:8.36 (1H,s,C=CH).^{13}C:143.03 (C=CH);118.51(C≡N);100.11 (C=CH). SM[EI,70 eV]:333([M-H]$^{+}$,100). Washing in hot hexane.Yield=67%.MP >260°C
11q	^{1}H: 8.39(1H,s,C=CH). ^{13}C: 142.97 (C=CH);118.51(C≡N);97.79 (C=CH).SM[EI,70 eV]:320([M]$^{+}$,31);319([M-H]$^{+}$,100).

	Washing in hot hexane.Yield=70%.MP >260°C
11r	^{1}H: 8.29(1H, s,C=C<u>H</u>). ^{13}C: 142.85 (C=<u>C</u>H);118.34(C≡N);97.79 (<u>C</u>=CH).SM[EI,70 eV]:350([M]$^{+}$,48);349([M-H] $^{+}$,100). Washing in hot hexane. Yield=50%.MP >260°C
11s	^{1}H: 8.42 (1H,s,C=C<u>H</u>). ^{13}C: 143.45 (C=<u>C</u>H); 117.69(C≡N);105.26 (<u>C</u>=CH). SM [EI, 70eV]: 335([M]$^{+}$,44). Washing in hot hexane.Yield=78%. MP =200-202°C
11t	^{1}H: 8.50 (1H, s, C=C<u>H</u>).^{13}C:143.19 (C=<u>C</u>H);118.71(C≡N);103.20 (<u>C</u>=CH). SM [EI,70 eV]:324([M]$^{+}$,58); 323([M-H]$^{+}$,100). Washing in hot hexane.Yield=24%. MP =238-240°C
11u	^{1}H: 8.61 (1H, s, C=C<u>H</u>). ^{13}C:143.31(C=<u>C</u>H); 118.87(C≡N); 107.18 (<u>C</u>=CH). SM [EI,70 eV]:358([M-H]$^{+}$,13). Recrystallization from ethanol. Yield=79%.MP >260°C
11v	^{1}H: 8.29 (1H,s,C=C<u>H</u>). ^{13}C:143.40(C=<u>C</u>H); 118.21(C≡N);101.62 (<u>C</u>=CH). SM[EI,70 eV]:368([M]$^{+}$,87). Washing in hot hexane. Yield= 50%. MP >260°C
11w	^{1}H: 8.45 (1H,s,C=C<u>H</u>).^{13}C:145.11 (C=<u>C</u>H);116.10(C≡N);105.11 (<u>C</u>=CH). SM[EI,70eV]: 281([M-H] $^{+}$,100). Washing in hot hexane. Yield=48%.MP >260°C
11x	^{1}H:8.38 (1H,s,C=C<u>H</u>).^{13}C:143.17 (C=<u>C</u>H);115.11(C≡N);104.17 (<u>C</u>=CH). SM[EI,70eV]: 292([M-H] $^{+}$,100). Washing in hot hexane. Yield=38%.MP =254-256°C
13a	^{1}H: 13.05(2H,s, NH).^{13}C:185.77(C=O); 113.16(C≡N);64.09(NC-<u>C</u>=C). SM [IE,70eV]:262([M+H] $^{+}$,50). Recrystallization from acetic acid. Yield=60%.MP >260°C
13b	^{1}H:13.05(2H,s, NH).^{13}C:185.27(C=O); 113.16(C≡N);64.09(NC-<u>C</u>=C). SM [IC,NH3]:292([M+H] $^{+}$,100). Washing in hot ethanol. Yield=22%.MP =250°C
13c	^{1}H: 12.97(2H, s,NH). ^{13}C:184.79(C=O); 114.06(CN); 64.89(NC-<u>C</u>=C).SM[IC, NH3]:296([M+H] $^{+}$,100). Washing in hot ethanol. Yield=59%.MP >260°C
13d	^{1}H: 13.05(2H,s, NH).^{13}C:184.89 (C=O);114.76(CN); 64.68(NC-<u>C</u>=C). SM [IE, 70eV]:279([M]$^{+}$,77). Washing in hot ethanol. Yield=62%.MP >260°C
13e	^{1}H: 13.05 (2H,s, NH).^{13}C:185.26 (C=O);114.17 (CN);64.09 (NC-<u>C</u>=C).SM [IC,NH3]:305([M-H] $^{+}$,100). Recrystallization from ethanol. Yield=36%.MP =234-236°C
13f	^{1}H: 13.50(2H, s,NH).^{13}C:184.59 (C=O);113.98(C≡N); 65.18(NC-<u>C</u>=C).SM [IC,NH3]:306([M]$^{+}$,100). Washing in hot ethanol. Yield=30%.MP >260°C
13g	^{1}H: 13.25(2H,s, NH).^{13}C:185.41(C=O); 115.50(C≡N);65.76(NC-<u>C</u>=C). SM [IE, 70eV]:337([M+ H]$^{+}$, 45). Washing in hot ethanol. Yield=26%. MP =212-214°C
13h	^{1}H: 13.50(2H,s, NH).^{13}C:185.39(C=O); 114.61(C≡N);65.98(NC-<u>C</u>=C). SM [IE, 70 eV]: 339 ([M-H] $^{+}$, 20) [IC, NH3]: 341 ([M+H] $^{+}$, 100). Washing in hot ethanol.Yield=41%.MP =194°C
13i	^{1}H: 13.50(2H, s,NH).^{13}C: 185.41(C=O);115.12 (C≡N);65.76(NC-<u>C</u>=C). SM [IE, 70eV]:324([M]$^{+}$,29);323([M-H] $^{+}$,95). Washing in hot ethanol. Yield=32%.MP >260°C
13j	^{1}H: 13.58(2H,s, NH).^{13}C:185.45 (C=O);115.12(CN); 65.76(NC-<u>C</u>=C). SM [IE, 70eV]:202([M+-(COΦNO2)]$^{+}$,100).

	Washing in hot ethanol.Yield=30%. MP = 234-236°C
18a	^{1}H:7.80(1H,d,J=15.6Hz,CH=CH);7.50(1H,d,J=15.6Hz,CH=CH);2.89(3H,s,CH_3).^{13}C:179.50CO);151.98CN),141.56(CH=CH);121.69(CH=CH);18.36(CH_3).ES$^+$SM:263[M+H$^+$]. Recrystallization from MeCN/H_2O(1:1).Yield=80%.MP =156-158°C
18b	^{1}H:7.75(1H,d,J=16Hz,CH=CH);7.48(1H,d,J=16Hz,CH=CH);2.89(3H,s,CH_3).^{13}C:179.35CO);152.04CN);141.50(CH=CH);121.70(CH=CH);18.12(CH_3).ES$^+$SM:277[M+H$^+$]. Recrystallization from cyclohexane.Yield=70%.MP =153-155°C
18c	^{1}H:7.75(1H,d,J=16Hz,CH=CH);7.48(1H,d,J=16Hz,CH=CH);2.89(3H,s,CH_3).^{13}C:179.35CO);152.04CN);141.50(CH=CH);121.70(CH=CH);18.12(CH_3).ES$^+$SM:277[M+H$^+$]. Recrystallization fromcyclohexane.Yield=70%.MP =153-155°C
18d	^{1}H:7.75(1H,d,J=16Hz,CH=CH);7.54(1H,d,J=16Hz,CH=CH);2.81(3H,s,CH_3).^{13}C:179.22CO);152.07CN);141.57(CH=CH);121.77(CH=CH);18.09(CH_3).ES+SM: 277[M+H$^+$]. Recrystallizationfrom hexane/DCM(3:1).Yield=71%.MP =127-130°C
18e	^{1}H:7.75(1H,d,J=16Hz,CH=CH);7.48(1H,d,J=16Hz,CH=CH);2.89(3H,s,CH_3).^{13}C:179.36CO);151.98CN);141.56(CH=CH);121.70(CH=CH);18.10(CH_3).ES+SM: 277[M+H$^+$]. Recrystallizationfrom cyclohexane.Yield=68%.MP=151-153°C
18d	^{1}H:7.78(1H,d,J=15.8Hz,CH=CH);7.45(1H,d,J=15.8Hz,CH=CH);2.89(3H,s,CH_3).^{13}C:179.36CO);151.98CN);141.56 (CH=CH);121.70(CH=CH);18.10(CH_3).ES$^+$SM:305[M+H$^+$]. Recrystallization from hexane. Yield=58%.MP =132-135°C
18f	^{1}H:7.80(1H,d,J=15.6Hz,CH=CH);7.38(1H,d,J=15.6Hz,CH=CH);2.78(3H,s,CH_3).^{13}C:179.50CO);151.95CN);141.56(CH=CH);120.89(CH=CH;18.26(CH_3). ES$^+$SM:279[M+H$^+$]. Recrystallization from ethanol.Yield=56%.MP >260°C
18g	^{1}H:7.85(1H,d,J=15.7Hz,CH=CH);7.36(1H,d,J=15.6Hz,CH=CH);2.68(3H,s,CH_3).^{13}C:178.50CO);152CN);139.56 (CH=CH);121.88(CH=CH);16.96(CH_3).ES$^+$SM:279[M+H$^+$]. Recrystallization from H_2O-ethanol. Yield=59%.MP >260°C
18h	^{1}H:7.89(1H,d,J=15.6Hz,CH=CH);7.52(1H,d,J=15.6Hz,CH=CH);2.88(3H,s,CH_3).^{13}C:180.39CO);151.43CN);141.97 (CH=CH);121.88(CH=CH);18.10(CH_3).ES$^+$SM:279[M+H$^+$]. Recrystallization from ethanol. Yield= 57%.MP >260°C
18i	^{1}H:7.78(1H,d,J=16Hz,CH=CH);7.45(1H,d,J=16Hz,CH=CH);2.85(3H,s,CH3).13C:179.36(C=O);151.98(C=N);141.46 (CH=CH);121.70(CH=CH);18.10(CH3). ES$^+$SM:306[M+H$^+$]. Recrystallization from H_2O.Yield=30%.MP =197-200°C
18j	^{1}H:7.72(1H,d,J=15.6Hz,CH=CH);7.50(1H,d,J=15.6Hz,CH=CH);2.80(3H,s,CH_3).^{13}C:179.30CO);152.05CN);141.22 (CH=CH);120.90(CH=CH);18.20(CH_3).ES$^+$SM:293[M+H$^+$].Recrystallization from hexane/DCM(3:1).Yield=71%.MP =196-198°C
18k	^{1}H:7.72(1H,d,J=15.6Hz,CH=CH);7.50(1H,d,J=15.6Hz,CH=CH);2.80(3H,s,CH_3).^{13}C:179.30CO);152.05CN);141.22 (CH=CH);120.92(CH=CH);18.03(CH_3).ES$^+$SM:293[M+H$^+$]. Recrystallization from hexane/DCM(3:1).Yield=70%.MP =127-129°C
18l	^{1}H:7.72(1H,d,J=15.6Hz,CH=CH);7.48(1H,d,J=15.6Hz,CH=CH);2.79(3H,s,CH_3).^{13}C:179.41(C=O);151.70(C=N);141.52(CH=CH);121.89(CH=CH);18.11(CH_3).ES$^+$SM:293[M+H$^+$]. Recrystallization from ethyl acetate. Yield=73%.MP=158-160 °C
18m	^{1}H:7.66(1H,d,J=15.6Hz,CH=CH);7.33(1H,d,J=15.4Hz,CH=CH);2.81(3H,s,CH_3).^{13}C:179.45(C=O);148.90(C=N);141.92(CH=CH);121.89(CH

	=CH);18.0(CH3). ES^+SM:323[$M+H^+$]. Recrystallization from hexane/DCM(3:1).Yield=70%.MP =169-171°C
18n	^{1}H:7.66(1H,d,J=15.6Hz,CH=CH);7.35(1H,d,J=15.4Hz,C<u>H</u>=CH);2.80(3H,s,CH3).^{13}C:179.60(C=O);146.49(C=N);41.92(CH=<u>C</u>H);121.89(<u>C</u>H=CH);18.16(CH3).ES^+SM:323[$M+H^+$]. Recrystallization from hexane/DCM(3:1).Yield=86%.MP =165-167°C
18o	^{1}H:7.80(1H,d,J=15.3Hz,CH=CH);7.70(1H,d,J=15.3Hz,CH=CH);2.85(3H,s,CH3).13C:178.96(C=O);152.81(C=N);134.16 (CH=CH);121.88(CH=CH);18.13(CH3). ES^+SM:308[$M+H^+$]. Recrystallization from ethanol.Yield=65%.MP =219-221°C
18p	^{1}H:7.68(1H,d,J=15.3Hz,CH=C<u>H</u>);7.50(2H,d,J=15.3Hz,C<u>H</u>=CH);2.83(3H,s,CH3).^{13}C:178.06(C=O);153.01(C=N); 134.34(CH=<u>C</u>H);121.0(<u>C</u>H=CH);18.20(CH3). ES^+SM:308[$M+H^+$]. Recrystallization from butanol. Yield=80%.MP >260°C
18q	^{1}H:7.80(1H,d,J=15.6Hz,CH=C<u>H</u>);7.51(1H,d,J=15.9Hz,C<u>H</u>=CH);2.79(3H,s,CH3).^{13}C:180.0(C=O);152.62(C=N);139.85 (CH=<u>C</u>H);120.89(<u>C</u>H=CH);18.10(CH3).ES^+SM:297.75[$M+H^+$]. Recrystallization from hexane/DCM(3:1).Yield=72%.MP =173 -175°C
18r	^{1}H:7.68(1H,d,J=15.3Hz,CH=C<u>H</u>);7.58(1H,d,J=15.3Hz,C<u>H</u>=CH);2.73(3H,s,CH3).^{13}C:179.03(C=O);152.58(C=N); 139.84(CH=<u>C</u>H);121.85(<u>C</u>H=CH);18.13(CH3).ES^+SM:342[$M+H^+$]. Recrystallization from ethanol. Yield=84%.MP =207-209°C
18s	^{1}H:7.68(1H,d,J=15.3Hz,CH=C<u>H</u>);7.58(1H,d,J=15.3Hz,C<u>H</u>=CH);2.73(3H,s,CH3).^{13}C:180.03(C=O);152.58(C=N); 139.90(CH=<u>C</u>H);121.85(<u>C</u>H=CH);18.13(CH3).ES^+SM:281[$M+H^+$].Recrystallization from hexane/DCM(3:1).Yield=75%.MP =192-194°C
18t	^{1}H: 7.68 (1H, d, J = 15.3 Hz, CH=C<u>H</u>); 7.50 (2H, d, J = 15.3 Hz, C<u>H</u>=CH); 2.85 (3H, s, CHar). ^{13}C: 178.06 (C=O); 153.01 (C=N); 134.34 (CH=<u>C</u>H); 121.0 (<u>C</u>H=CH); 18.0 (CH_3). ES+ SM: 264 [M+H+]. Recrystallization from acetone/H_2O (1 :1). Yield= 44%. MP=210-212°C
18u	^{1}H: 7.69 (1H, d, J = 15.3 Hz, CH=C<u>H</u>); 7.55 (2H, d, J = 15.3 Hz, C<u>H</u>=CH); 2.75 (3H, s, CHar). ^{13}C: 179.06 (C=O); 154.01 (C=N); 132.34 (CH=<u>C</u>H); 122.10 (<u>C</u>H=CH); 18.11 (CH_3). ES+ SM: 253 [M+H+]. Recrystallization from ethanol. Yield= 39%. MP= 198-200°C

2.2.2. Anticandidosic assay

The seventy-one diaza-heteroaryl derivatives functionalized by Michaël acceptor and reference drugs (Chlormidaole, Ketoconazole and Fluconazole) were evaluated against a clinical strain of *Candida albicans* "27506" provided by the Center for Diagnosis and Research on AIDS and opportunistic diseases (CeDReS) in Abidjan. The screening of anticandidosic activities consisted of the determination of the Minimum Inhibitory Quantities (MIQs) following the bioautography method [**27**, **28**]. This is a method of in vitro determination by thin layer chromatography of the minimum quantities capable of inhibiting the proliferation of *Candida albicans*. The 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 Silicagel 60 F^{254} glass plates. Chromatograms were previously developed in saturated cuvettes of a chloroform-methanol-water mobile phase in a ratio (65:35:5) and then dried. In addition, *Candida albicans* fungal inoculum containing about 10^5 cells/mL was obtained by plating three colonies of a pure strain from 24 to 48 h in Tryptone Soy broth. This inoculum was then spread on each chromatogram. The plates were incubated at 30°C after solidification of the agar for 24 h. The resulting plates were then impregnated with an aqueous solution of Methylthiazolyl Tetrazolium Chloride (MTT) at a concentration of 2.5 mg/mL and incubated again for 2-4 h. Live fungal cells cause MTT to change color from yellow to purple due to the dehydrogenase activity of the mitochondria. The zones of growth inhibition subsequently appear as white spots on a purple background on the 254 nm UV slide. The MIQ corresponds to the smallest amount of products that led to an inhibition of fungal growth.

3. Results and discussion

The results obtained during the evaluation of the anticandidosic activities against *Candida albicans*, the diaza-heteroaryls functionalized by Michaël acceptors and the reference drug substances (Chlormidazole, Fluconazole and Ketoconazole) are gathered in Tables **2**, **3**, **4**, **5** and **6**. The activity of each product is given by its Minimum Inhibitory Quantity (MIQ) expressed in micrograms (µg).

Table 2: In vitro anticandidosic activities of the reference substances against *Candida albicans.*

References drugs substances	**MIQ (µg)** *(Candida albicans)*
Chlormidazole	10
Fluconazole	10
Ketoconazole	10

Table 3: In vitro anticandidosic activities of benzimidazolyl-arylpropenones against *Candida albicans.*

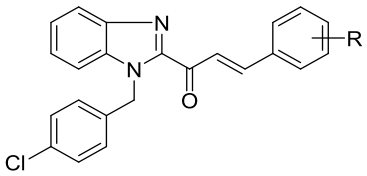
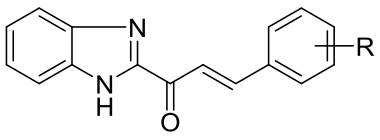
Chemical structures	Compounds	R	MIQ (µg) *(Candida albicans)*
	7a	H	10
	7b	3-CH_3	10
	7c	2-OH	10
	7d	3-OCH_3	10
	7e	4-Cl	10
	7f	4-Br	10
	7g	4-F	10
	7h	2-Cl, 5-NO_2	5
	7i	H	1,25
	7j	3-CH_3	0,625
	7k	2-OH	10
	7l	3-OCH_3	10
	7m	4-Cl	10
	7n	4-Br	10
	7o	4-F	0,625
	7p	2-Cl, 5-NO_2	10

Table 4: In vitro anticandidosic activities of benzimidazolyl-arylacrylonitriles against *Candida albicans.*

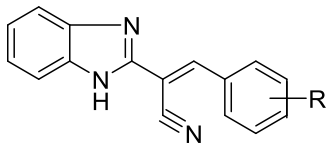
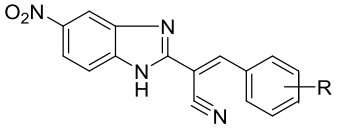
Chemical structures	Compounds	R	MIQ (µg) *(Candida albicans)*
	11a	H	10
	11b	4-CH_3	10
	11c	4-OH	10
	11d	4-$N(CH_3)_2$	10
	11e	4-OCH_3	10
	11f	2,5-diOCH_3	10
	11g	4-NO_2	10
	11h	3-Cl	10
	11i	2,4-diCl	10
	11J	4-Br	10
	11k		10
	11l		10
	11m	H	10
	11n	4-CH_3	10
	11o	4-OH	10
	11p	4-$N(CH_3)_2$	10
	11q	4-OCH_3	10
	11r	2,5-diOCH_3	10
	11s	4-NO_2	10
	11t	3-Cl	1,25
	11u	2,4-diCl	0,16
	11v	4-Br	0,16
	11w		10
	11x		10

Table 5: In vitro anticandidosic activities of benzimidazolyl-arylcyanopropénones against *Candida albicans.*

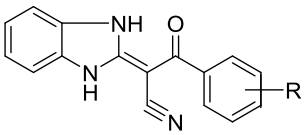
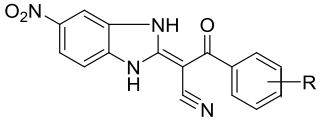
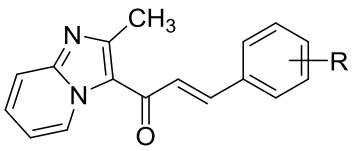
Chemical structures	Compounds	**R**	**MIQ (µg)** *(Candida albicans)*
	**13a**	H	10
	13b	OCH_3	10
	13c	Cl	10
	13d	F	10
	13e	NO_2	10
	**13f**	H	10
	13g	OCH_3	10
	13h	Cl	10
	13i	F	10
	13j	NO_2	0,625

Table 6: In vitro anticandidosic activities of imidazopyridinyl-arylpropénones against *Candida albicans.*

Chemical structures	Compounds	R	MIQ (µg) *(Candida albicans)*
	**18a**	H	2,5
	18b	2-CH_3	2,5
	18c	3-CH_3	2,5
	18d	4-CH_3	2,5
	18e	4-$CH(CH_3)_2$	0,31
	18f	2-OH	10
	18g	3-OH	1,25
	18h	4-OH	10
	18i	4-$N(CH_3)_2$	10
	18j	2-OCH_3	10
	18k	3-OCH_3	10
	18l	4-OCH_3	10
	18m	3,4-diOCH_3	10
	18n	2,5-diOCH_3	10
	18o	3-NO2	10
	18p	4-NO2	10
	18q	4-Cl	10
	18r	4-Br	1,25
	18s	4-F	5
	18t		10
	18u		10

The structure-activity relationship studies carried out allow establishing that the replacement of the methyl in position 2 of Chlormidazole by the phenylpropenone functional chain of the chalcones, leads to compound **7a** with an anti-*candida* activity of about 10µg. This anti-*candida* activity is superior to that of the reference drug substances and confirms the intrinsic anti-infectious potentialities of the benzimidazole nucleus and the phenylpropenone functional grouping of the chalcones [**29**-**31**]. In order to improve this anti-*candida* activity, different structural variants have been undertaken at the level of the benzene homocycle of propenone, the propenone chain and the benzimidazole heterocycle of compound **7a** (**Figure 3**).

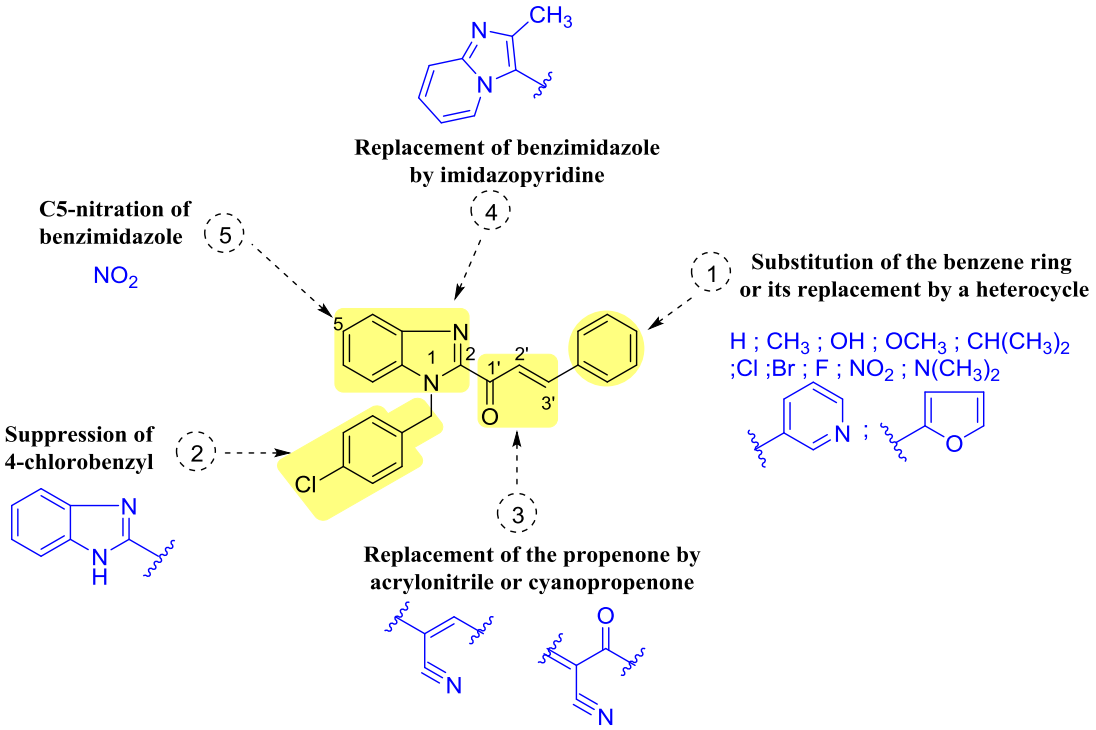


Figure 3: sites of structural variations undertaken around compound **7a**

3.1. Substitution or replacement of the benzene homocycle

The main variations undertaken on the homocycle of compound 7a allow establishing that the introduction of chemical modulators of methylated, hydroxylated, methoxylated and halogenated type compounds (**7b** - **7g**) on the benzene homocycle in position 3' of propenone is favourable to the maintenance of anti-*Candida* activities around 10 µg. This anti-*Candida* activity remains however superposable to that of compound **7a** and the reference drug substances. On the other hand, the concomitant presence of a chlorine atom and a nitro group on the benzene homocycle in the 3' position of propenone (compound **7h**) is conducive to the improvement of the anti-*Candida* activities with a MIQ of 5µg. This anti-*Candida* efficacy is 2 times higher than that of benzimidazolyl-phenylpropenone or compound **7a** and reference drugs.

3.2. Suppression of structural variations on the benzene homocycle

The deletion of the *para*-chlorobenzyl group of the benzimidazole of compound 7a leads to an increase in the anti-*candida* activity of compound **7i**. This compound with an MIQ of 1.25µg was found to be 8 times more potent than its *N*-*para* chlorobenzylated counterpart (compound **7a**, MIQ=10 µg). Furthermore, the deletion of the *para* chlorobenzylated and the introduction on the benzene homocycle of methyl (compound **7j**) or fluorine (compound **7o**) modulator leads to an exaltation of the antifungal efficacy of said compounds with MIQs at 0.625 µg. As in series of anthelmintic benzimidazoles, the non-substitution of the pyrrolic nitrogen seems to be also essential for good antifungal activities. The presence of the *para*-chlorobenzyl on the pyrrolic nitrogen essential for the antifungal properties of Chlormidazole is therefore not relevant in our series of benzimidazolyl-arylpropenones. On the other hand, the introduction of hydroxylated, methoxylated, chlorinated or brominated modulators (compounds **7k**, **7l**, **7m**, **7n**) leads to the maintenance of the anti-*candida* activities at 10 µg, despite the *para*-chlorobenzylated deletion.

3.3. Replacement of propenone by an acrylonitrile

The anticandidosic results show that the replacement of propenone of compound **7i** by another Michaël acceptor of acrylonitrile type, leads to benzimidazolyl-phenylacrylonitrile or compound **11a**, whose anti-*candida albicans* activities at 10 µg are equivalent to those of the reference drug substances. To improve the said activities, the various structural variations undertaken around compound **11a** make it possible to establish that the introduction of a modulator of methyl, hydroxyl, methoxyl, *N*,*N*-dimethylamine, nitro, halogen (bromine, chlorine) type on the benzene homocycle (compounds **11b** - **11j**) or even its replacement by heteroaryls of furan

(compound **11k**), pyridine (compound **11l**) type leads to the maintenance of the quantity necessary to inhibit the proliferation of *Candida albicans* at 10 µg. Moreover, the substitution of benzimidazole in position 5 by a nitro group (NO_2) and the maintenance of the pharmacochemical modulators preceding lead to the maintenance or improvement of the antifungal activities. Thus, the C5-nitration of benzimidazole (compound **11m**) or the C5-nitration of benzimidazole associated with the presence on the benzene homocycle of a chemical modulator of methyl, hydroxyl, methoxyl, *N*,*N*-dimethylamine, nitro (compounds **11n - 11v**) or the C5-nitration of benzimidazole coupled with the replacement of the benzene homocycle by heteroaryls of the furan type (compound **11w**), pyridine (compound **11x**) proved to be insufficient to improve the anti-*candida* activities beyond 10 µg. On the other hand, the C5 nitration of benzimidazole associated with the presence of chlorine on the benzene homocycle (compound **11t**) leads to an increase in the anti-candida albicans activity with an MIQ at 1.25 µg. Moreover, the duplication of this chlorine atom (compound **11u**) or its replacement by a bromine atom (compound **11v**), leads to the exaltation of the antifungal activities with an MIQ at 0.16 µg. Such anti-*candida* performance is 62.5 times higher than the references drugs substances (MIQ = 10 µg**).**

3.4. Replacement of propenone by a cyanopropenone

The combination of the previous functional groups namely propenone from compound **7i** and acrylonitrile from compound **11a** provided a new cyanopropenone functional group. The anti-*candida* results obtained allow to establish that the association of propenone and acrylonitrile in benzimidazolyl-phenylcyanopropenone or compound **13a**, did not improve the antifungal efficacy, since the amount necessary to inhibit the fungal growth remains at 10 µg. Structural variations undertaken in this chemistry to improve the anti-*candida* activities showed that the presence of chemical modulators of methoxyl (compound **13b**), halogens (chlorine, fluorine) (compounds **13c**-**13d**) and nitro (compound **13e**) contribute to the maintenance of anti-*candida* activities at 10µg. Similarly, the double modulation, to know the blocking of position 5 by a nitro group (NO_2) and the presence of chemical modulators of methoxyl, halogen (chlorine, fluorine) type (compound **13f**-**13i**) on the benzene homocycle of cyanopropenone leads to the same type of anti-*candida* results (MIQ=10µg). On the other hand, the concomitant presence of a nitro group in position 5 of the benzimidazole and in position 4 of the benzene homocycle (compound **13j**) leads to an improvement of the antifungal activities. This compound **13j** with an MIQ of 0.625 µg was found to be 16 times more effective than the reference drug substances.

3.5. Replacement of benzimidazole by an imidazopyridine

The anti-*candida* results obtained established that the replacement of the benzimidazole heterocycle by another imidazopyridine diaza-heteroaryl leads to compound **18a**, which showed anti-*candida* performance at 2.5 µg. Such an anticandidosic efficacy 4 times higher than the reference drug substances (MIQ=10 µg) demonstrates that imidazopyridine can validly replace benzimidazole and corroborates the anti-infectious potentialities of the said core [**32**-**34**]. Furthermore, the structural variations undertaken revealed that the presence of a methyl group (compounds **18b**; **18c**; **18d**), whatever its isomeric position on the benzene rings, led to the same efficacy of 2.5 µg as compound **18a**. On the other hand, the presence on the benzene ring of another alkyl group of isopropyl nature (compound **18e**), led to an exaltation of the antifungal activities with an MIQ of 0.31 µg. Such an effective inhibitory amount is 8 times higher than that of compound **18a** from which this derivative was derived. The introduction of a hydroxyl group on the benzene homocycle, showed that contrary to the methyl group, the isomeric position of this strongly electron-donating modulator influences the improvement of the desired anti-*candida* activities. Indeed, the *ortho* and *para*-hydroxylated isomers (compounds **18f**; **18h**) did not induce an improvement of the anticandidosic efficacy. These remained at 10 µg as the reference drug substances. On the other hand, the meta-hydroxy isomer (compound **18g**), presented an MIQ of 1.25 µg, to knowa performance 8 times higher than that of the reference drug substances. As for the presence on the benzene ring of a dimethylamine group (compound **18i**), a nitro group (compounds: **18o**; **18p**) or even a methoxyl group (compounds: **18j**; **18k**; **18l**) or its duplication (compounds **18m**; **18n**), it leads to the maintenance of anti-*Candida albicans* activities with MIQs at 10 µg. The halogenation in *para* isomeric position of the benzene ring to mimic that of the medicinal antifungal azoles, revealed that the presence of a chlorine atom (compound **18q**) would not be essential for the induction of a good anticandidosic activity since the MIQ remained at 10 µg. On the other hand, the *para*-fluorination of the benzene homocycle (compound **18s**) leads to a better activity compared to the chlorinated derivative with an MIQ of 5 µg. Paradoxically, only the bromine atom (compound **18r**) was able to induce by its presence on the benzene, a clear improvement of the activities. Indeed, the brominated derivative with an MIQ of 1.25 µg, showed an antifungal performance 8 times

higher than those of the reference drug substances. The application of the pharmacochemical concept of ring isostery by replacing the benzene ring with heteroaryls of pyridine (compound **18t**) or furanic (compound **18u**) nature, led to the maintenance of anticandidosic activities at 10 µg.

4. Conclusion

This study has provided a better understanding of the structure-anticandidosic activity relationships in series of diaza-heteroaryls functionalized with propenone, acrylonitrile and cyanopropenone Michaël acceptors. Thus, in the benzimidazolyl-arylpropenone series, the improvement of the activities against *Candida albicans* is subject to the suppression of the *para*-chlorobenzyl fixed on the pyrrolic nitrogen of the benzimidazole nucleus coupled or not with the presence of a methylated or a fluorinated atom on the benzene homocycle in the 3' position of the propenone. As for the chemical series of benzimidazolyl-arylacrylonitriles, the improvement of said activities also requires a double chemical modulation, namely the presence of a nitro group on the potential metabolization site C5 of the benzimidazole and the presence of a halogenated atom (bromine, chlorine) at the isomeric positions 2, 3 or 4 of the benzene homocycle of the acrylonitrile. As before, the improvement of the serial anti-*candida* activities of the benzimidazolyl-arylcyanopropenones requires the presence of a nitro group in position 5 of the benzimidazole and in position 4 of the benzene homocycle of the cyanopropenone. Finally, in the chemical series of imidazopyridinyl-arylpropenones, it appears that the improvement of the anticandidosic activities is achieved by the introduction of an isopropyl or hydroxyl group or a bromine atom respectively in position 4, 3 and 4 on the benzene homocycle in position 3' of the propenone. These structure-activity studies offer prospects for the pharmacochemical development of new anti-*candida* agents with a diaza-heteroaryl structure functionalized by Michaël acceptors.

Abbreviation section

MIQ	Minimum Inhibitory Quantity
MTT	Methylthiazolyl Tetrazolium
CeDReS	Center for Diagnosis and Research on AIDS and opportunistic diseases

Conflict of interest

Authors have none to declare.

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