Full Paper

Synthesis and Anti-*Candida* Potential of Certain Novel 1-[(3-Substituted-3-phenyl)propyl]-1*H*-imidazoles

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The synthesis and anti-*Candida* activity of 1-[(3-aroyloxy-3-phenyl)propyl]-1*H*-imidazoles **5a–f** and 1-[(3-alkyl/aralkyl/phenyl-3-phenyl)propan-3-ol]-1*H*-imidazoles **5g–j** are reported. The influence of the ester formation and different substitutions on the anti-*Candida* activity of the alcohol **4** was investigated. Among the newly developed bioactive chemical entities, compounds **5b** and **5c** displayed minimum inhibitory concentrations (MICs) against *Candida albicans* and *Candida pseudotropicales* comparable to that of tioconazole and more potent than miconazole.

Keywords: Anti-*Candida* / Grignard reaction / Imidazoles / Mannich reaction

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Introduction

A significant increase in fungal infections has been observed over the past two decades. Many reports of invasive topical and systemic infections caused by the opportunistic pathogen *Candida* species are always associated with the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer and anti-AIDS drugs [1]. One of the major problems in the treatment of *Candida* infections is the spread of antifungal drug resistance mainly in patients chronically subjected to antimycotic therapy such as HIV-infected patients [2, 3].

Antifungal drugs are mainly classified into five major classes: Azoles, polyenes, allylamines, thiocarbamates, and fluoropyrimidines [4]. Azole class is commonly used as antifungal agent specially for *Candida* infections as many marketed drugs containing the azole moiety, e.g. ketoconazole, itraconazole, econazole, miconazole, tioconazole, and fluconazole are used as antifungal drugs [5]. Also, the imidazole fluxetine analogue **I** [6] has been found to possess anti-*Candida* activity and the imidazole derivatives **II–IV** (Fig. 1) exhibited potent antifungal activity against *Candida albicans* and dermatophytes [5]. On the other hand, the therapeutic use of many antifungal drugs is often accompanied by some drawbacks like drug resistance specially in chronic patients [2, 3] as well as unwanted side effects and limited bioavailability [7, 8]. Accordingly, the need for new antifungal drugs has prompted intensive research worldwide.

In a previous work [9], it was reported that the alcohol **4** exhibited antifungal activity against human and animal pathogens. Therefore, compound **4** would serve as prototypic molecule for subsequent molecular modifications.

Based upon the aforementioned premises, we became interested toward the development of novel bioactive drug-like candidates namely, the esters 1-[(3-aroyloxy-3-phenyl)-propyl]-1-*H*-imidazoles **5a–f**, and the tertiary alcohols 1-[(3-alkyl/aralkyl/phenyl-3-phenyl)propan-3-ol]-1-*H*-imidazoles **5g–j** to be screened as anti-*Candida* agents (Fig. 2). The influence of the lipophilic nature of the ester functionality in

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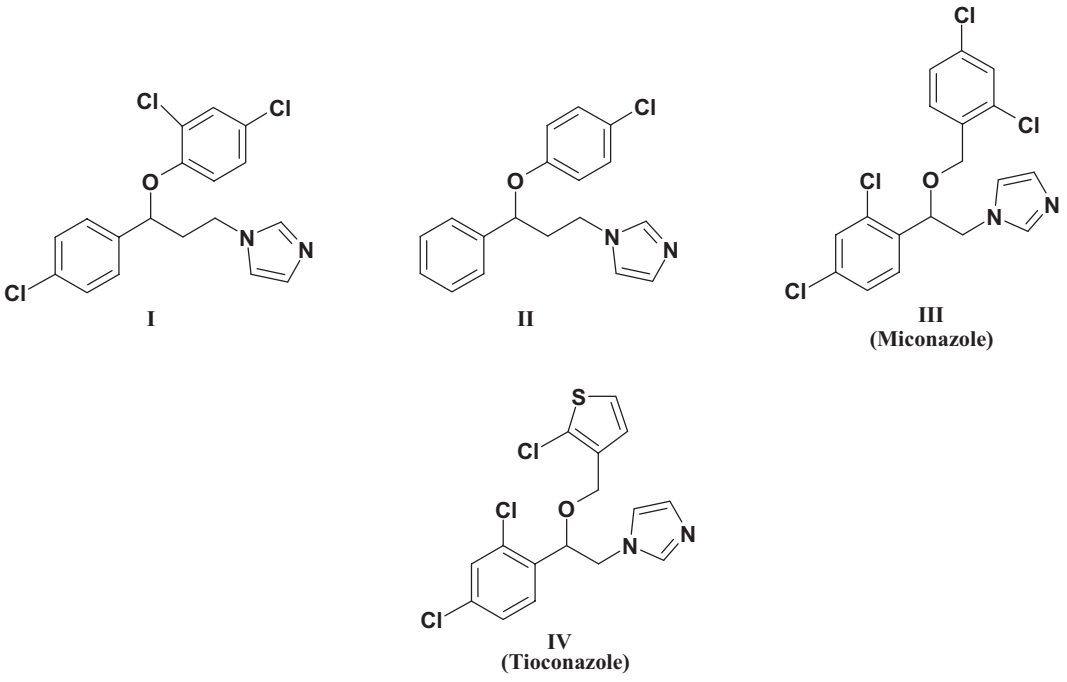


Figure 1. Imidazoles as antifungal agents.

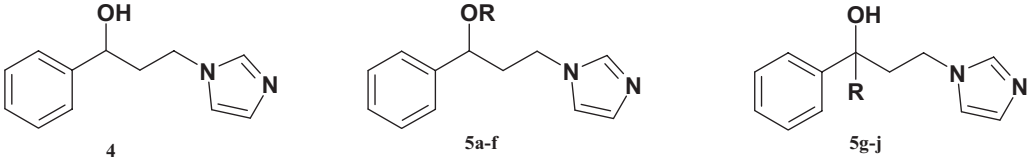


Figure 2. The prototype imidazole alcohol **4**, the corresponding esters **5a–f** and tertiary alcohols **5g–j**.

compounds **5a–f** as well as alkyl, phenyl, or aralkyl substitutions in alcohols **5g–j** on the anti-*Candida* activity of the alcohol **4** was investigated.

Results and discussion

Synthesis

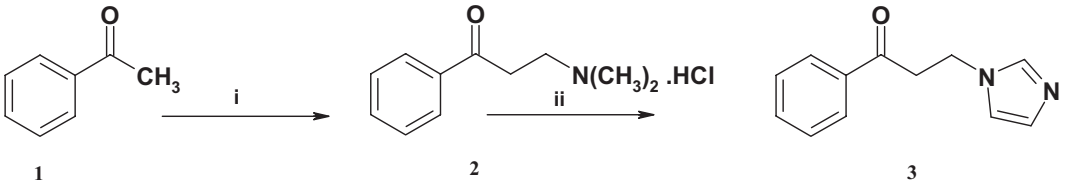
Synthetic pathways for the synthesis of the target compounds **5a–j** have been illustrated in Schemes 1 and 2. Thus, the Mannich base hydrochloride **2** was prepared according to the reported procedure [10] using acetophenone, paraformaldehyde, and dimethylamine hydrochloride in the presence of 2 μL conc. HCl/mmol acetophenone in small amount of ethanol. Subsequently, compound **2** was subjected to nucleophilic substitution with imidazole in water to afford the ketone **3** [9] in 77% yield (Scheme 1).

Ketone **3** was elaborated to the alcohol **4** by adopting sodium borohydride reduction in methanol [9]. The produced alcohol **4** was esterified using the appropriate acid chloride and triethylamine in benzene to furnish the respective esters **5a–e** in moderate yields. The nitro ester **5e** was hydrogenated under normal pressure in the presence of PtO_2 at room temperature to yield the respective amino derivative **5f** (Scheme 2).

Furthermore, Grignard reaction was employed on the ketone **3** and the proper Grignard reagent in diethyl ether to give the corresponding tertiary alcohols **5g–j** in 32–71% yields (Scheme 2).

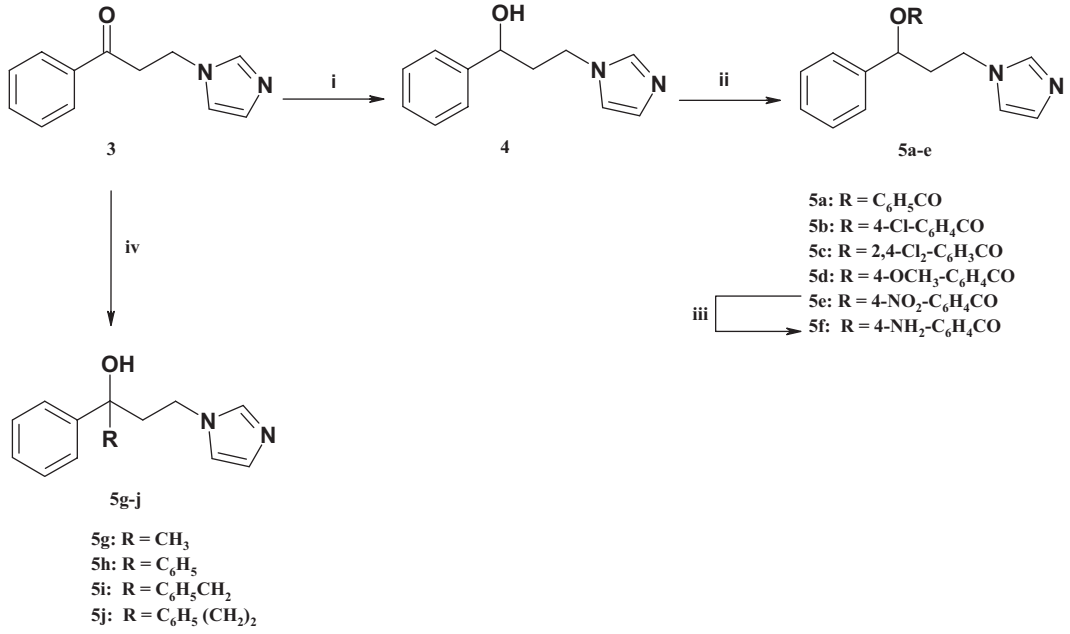
Biological evaluation

Table 1 displays the anti-*Candida* activity of the tested compounds **4** and **5a–j**, and of miconazole and tioconazole, taken as reference drugs, on *Candida albicans* and *Candida pseudotropicales*, which are important human pathogenic fungi, measured as minimum inhibitory concentration (MIC, μg/mL).



Reagents: (i) $HN(CH_3)_2 \cdot HCl$, $(CH_2O)_n$, conc. HCl, ethanol, reflux, 2 h. (ii) Imidazole, water, reflux, 5 h.

Scheme 1. Synthesis scheme for **3**.



Reagents: (i) $NaBH_4$, methanol, reflux, 3 h. (ii) Aroyl chloride, triethylamine, benzene, reflux, 18 h. (iii) H_2/PtO_2, THF, rt, 2 h. (iv) Mg, alkyl/aryl or aralkyl halide, diethyl ether, reflux, 18 h.

Scheme 2. Synthesis scheme for **5a–f** and **5g–j**.

Walker and Hills [9] documented the antifungal activity of the alcohol **4**. Accordingly, we focused our attention on the synthesis of the lipophilic 3-(1*H*-imidazol-1-yl)-1-phenylpropyl-4-benzoates **5a–f** to verify the effect of esterification of the free OH group of **4** on the anti-*Candida* activity. Compound **5a** showed anti-*Candida* activity (MIC = 1.5 μg/mL) which is nearly seven-fold greater than that of the alcohol **4** (MIC = 10 μg/mL) thus suggesting the lipophilic nature of this ester functionality to be responsible for the increase of anti-*Candida* activity. Nonetheless, the inhibitory potency of **5a** differs significantly from those of miconazole (MIC = 0.5 μg/mL) and tioconazole (MIC = 0.3 μg/mL). We therefore attempted to improve the anti-*Candida* potential of **5a** by substituting the phenyl moiety of the ester functionality of **5a** with substituents endowed with different electronic and steric properties. These substituents may be able to favor interaction with the structures of the target enzyme, the fungal cytochrome P450 14α-lanosterol demethylase ($P450_{14DM}$), leading to inhibition of the ergosterol formation in the fungal cell membrane [11]. In addition, these substituents could improve the bioavailability and the *in vivo* anti-*Candida* activity of the newly synthesized bioactive chemical entities which had been already observed in the class of antifungal azoles [12].

Halogen substitution, like chlorine in compounds **5b** and **5c**, is very useful to modulate the electronic effects on phenyl ring and may also influence the steric characteristics and the hydrophilic–hydrophobic balance of the molecules. Thus, the chlorinated esters **5b** and **5c** showed the best anti-*Candida* profile of the whole synthesized series exhibiting

Table 1. The antifungal activities of the tested compounds **4** and **5a–j** against *Candida albicans* and *Candida pseudotropicales*.

Compound No.	MIC*	*Candida albicans*		*Candida pseudotropicales*	
	(μg/mL)	Mean ± SD**	LSD***	Mean ± SD**	LSD***
4	10.0	13.7 ± 1.53	**5b**, **5c**	14.0 ± 1.00	**5b**, **5c**
5a	1.5§	13.0 ± 1.00	**5b**, **5c**	14.7 ± 1.53	**5b**, **5c**
5b	0.3	16.2 ± 1.76	**4**, **5a**, **5e-j**, **III** & **IV**	17.2 ± 1.76	**4**, **5a**, **5e-j**, **III** & **IV**
5c	0.3	17.2 ± 1.04	**4**, **5a**, **5e-j**, **III** & **IV**	18.2 ± 1.76	**4**, **5a**, **5e-j**, **III** & **IV**
5d	0.4	14.2 ± 1.76	**5c**	15.2 ± 1.76	**5c**
5e	75.0	12.7 ± 1.53	**5b**, **5c**	13.3 ± 1.53	**5b**, **5c**
5f	5.0	13.7 ± 1.53	**5b**, **5c**	14.5 ± 1.50	**5b**, **5c**
5g	20.0	12.0 ± 1.00	**5b**, **5c**	13.0 ± 1.00	**5b**, **5c**
5h	7.5	12.7 ± 1.53	**5b**, **5c**	13.0 ± 1.00	**5b**, **5c**
5i	7.5	13.0 ± 1.00	**5b**, **5c**	13.3 ± 1.53	**5b**, **5c**
5j	5.0	13.8 ± 1.26	**5b**, **5c**	14.3 ± 0.76	**5b**, **5c**
Miconazole (**III**)	0.5	13.3 ± 1.53	**5b**, **5c**	14.0 ± 1.00	**5b**, **5c**
Tioconazole (**IV**)	0.3	13.8 ± 1.26	**5b**, **5c**	14.5 ± 0.50	**5b**, **5c**

For *Candida albicans* *F*-ratio = 3.178, $P = 0.005$ and for *Candida pseudotropicales* *F*-ratio = 4.033, $P < 0.0001$.*The lowest concentration of the compound that produced complete microbial growth inhibition (μg/mL) against *Candida albicans* and *Candida pseudotropicales*. **The arithmetic mean of the inhibition zone diameters in mean ± standard deviation. ***Least significant differences (LSD). §MIC of **5a** was 1.0 μg/mL for *Candida pseudotropicales*.

MIC = 0.3 μg/mL which is nearly 33 fold greater than that of the alcohol **4** and were equipotent with the reference compound tioconazole (MIC = 0.3 μg/mL) while they were more potent than miconazole (MIC = 0.5 μg/mL). Moreover, the mean of the inhibition zones of compounds **5b** and **5c** against *Candida albicans* and *Candida pseudotropicales* was significantly larger than that of all other compounds whereas there was no significant difference between the activity of compounds **5b** and **5c** against both organisms (Table 1).

On the other hand, incorporation of hydrogen-bonding acceptor endowed with positive mesomeric effect on phenyl rings, such as methoxy group in compound **5d**, may be able to improve the inhibitory potency by increasing the affinity toward the enzyme-recognizing sites. Thus, the *para*-methoxy derivative **5d** displayed MIC = 0.4 μg/mL which is 25 fold more potent than the alcohol **4** as anti-*Candida*. On the contrary, substitution of the phenyl ring of the ester functionality with a strong electron withdrawing group endowed with negative mesomeric effect as hydrogen-bonding acceptor, such as nitro group in **5e**, does not seem to be practically favorable, causing a dramatic decrease in the anti-*Candida* activity with MIC = 75 μg/mL. However, reduction of the nitro group in **5e** to afford the respective amino derivative **5f** improves the anti-*Candida* properties of **5e** suggesting that the enzyme-recognizing sites contains hydrogen-bonding acceptor residues in the region corresponding to the position containing NO_2/NH_2 groups of the tested compounds. Compound **5f** displayed MIC = 5 μg/mL which is 15 times more potent than the nitro analogue **5e** and two times more potent than the alcohol **4** as anti-*Candida*.

The tertiary alcohols **5g–j** exhibited anti-*Candida* potential in the following descending order: **5j** > **5h** = **5i** > **5g** indicating that the lipophilic phenethyl moiety in the alcohol **5j** seems to be the favorable substituent for exerting the anti-*Candida* activity of the alcohols **5g–j**. Alcohol **5j** (MIC = 5 μg/mL) is two-fold more potent than the alcohol **4** and equipotent with the ester **5f** as anti-*Candida*. However, replacing the phenyl/aralkyl moieties of **5h–j** with methyl group to afford the alcohol **5g** (MIC = 20 μg/mL) led to four-fold decrease in the anti-*Candida* activity as compared to the alcohol **5j**.

Conclusion

This study was undertaken to evaluate the effects on the anti-*Candida* activity of the esterification of the OH group of the previously reported antifungal alcohol **4**. The obtained data revealed that the anti-*Candida* activity of the alcohol **4** was increased substantially through lipophilic esterification especially with chlorinated benzoic acids to give the esters **5b** and **5c** which are equipotent with the reference antifungal tioconazole and more potent than miconazole. There was no significant difference between compounds **5b** and **5c** against *Candida albicans* and *Candida pseudotropicales*. Also, the newly synthesized esters **5a–f** could be considered as prodrugs which may improve the pharmacokinetics and hence the bioavailability of the alcohol **4** leading to enhancement of its *in vivo* anti-*Candida* activity. In addition, the phenethyl

derivative **5j** of the alcohol **4** displayed a two-fold increase in the anti-*Candida* activity as compared to the alcohol **4**.

Experimental section

General

All melting points were determined using Electrothermal Capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin film (for oils) in NaCl discs or as KBr pellets (for solids) with JASCO FT/IR-6100 spectrometer and values are represented in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were carried out on Jeol ECA 500 MHz spectrophotometer using TMS as internal standard and chemical shift values were recorded in ppm on δ scale. The ^{1}H-NMR data were represented as follows: Chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), and number of protons. The ^{13}C-NMR data were represented as chemical shifts and type of carbon. EI mass spectra were determined on a Finnigan Mat SSQ-7000 spectrophotometer and Jeol JMS-AX 500. Elemental analyses were carried out at the Microanalytical Centre, Cairo University, Egypt. Silica gel TLC (thin layer chromatography) cards from Merck (silica gel precoated aluminum cards with fluorescent indicator at 245 nm) were used for thin layer chromatography. Visualization was performed by illumination with UV light source (254 nm). Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck.

*Preparation of 3-(dimethylamino)-1-phenylpropan-1-one hydrochloride **2***

Compound **2** was synthesized according to [10], mp 152–154°C ([10] 153°C), and its spectral data were consistent with those previously published [10].

*Preparation of 3-(1H-imidazol-1-yl)-1-phenylpropan-1-one **3***

A solution of **2** (21.4 g, 100 mmol) and imidazole (13.6 g, 200 mmol) in water (100 ml) was heated at 100°C for 5 h. The cooled reaction mixture was filtered and the collected solid was dried to furnish **3** (15.4 g, 77%) as a white solid, mp 95–97°C ([9] 96–99.5°C), and it was pure enough to be used in the next step without any purification.

*Preparation of 3-(1H-imidazol-1-yl)-1-phenylpropan-1-ol **4***

Compound **4** was synthesized according to [9], mp 107–109°C ([9] 106.5–108°C).

*General procedure for the preparation of the substituted aroyl esters **5a–e***

To an ice-cold mixture of the imidazole alcohol **4** (1.01 g, 5.0 mmol) and triethylamine (0.55 mL, 0.6 g, 6.0 mmol) in dry benzene (15 mL) was added the appropriate acid chloride (6.0 mmol) in dry benzene (5 mL) dropwise. The reaction mixture was refluxed for 18 h then cooled, filtered and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and 10% sodium bicarbonate solution. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford the aroyl esters **5a–d** as oils which were purified by column chromatography using chloroform/methanol (9.5:0.5) and the ester **5e** as a yellow solid which was recrystallized from ethyl acetate.

*3-(1H-Imidazol-1-yl)-1-phenylpropyl-4-benzoate **5a***

Yield 60%; pale yellow viscous oil; IR (KBr): ν (cm^{-1}) 3109, 3064, 1717 (C=O), 1506, 1270, 710; ^{1}H-NMR ($CDCl_3$): δ 2.38–2.39 (m, 1H, −C*H*$_2$−CH$_2$−N), 2.56–2.57 (m, 1H, −C*H*$_2$−CH$_2$−N), 4.03–4.04 (m, 2H, −CH$_2$−C*H*$_2$−N), 5.97–5.99 (m, 1H, C$_6$H$_5$−C*H*−O−), 6.91 (s, 1H, −N−C*H*=CH−N=), 7.05 (s, 1H, −N−CH=C*H*−N=), 7.36–7.45 (m, 9H, −N−C*H*=N−, H$_{ar.}$), 8.05 (d, J = 8.1 Hz, 2H, H$_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 37.9 (−*C*H$_2$−CH$_2$−N), 43.5 (−CH$_2$−*C*H$_2$−N), 73.7 (C$_6$H$_5$−*C*−O−), 118.8 (−N−*C*H=CH−N=), 126.4, 128.6, 128.9, 129.7, 129.8, 129.9 133.5 (−N−CH=*C*H−N=, CH$_{ar.}$, C$_{ar.}$), 137.1 (−N−*C*H=N−), 139.3 (C$_{ar.}$), 165.7 (C=O); MS *m*/*z* (%): 306 (M$^+$, 21), 201 (100), 105 (50), 77 (33); Anal. calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.38; H, 5.90; N, 9.21.

*3-(1H-Imidazol-1-yl)-1-phenylpropyl-4-chlorobenzoate **5b***

Yield 60%; pale yellow viscous oil; IR (KBr): ν (cm^{-1}) 3108, 2947, 1717 (C=O), 1501, 1271, 755; ^{1}H-NMR ($CDCl_3$): δ 2.35–2.37 (m, 1H, −C*H*$_2$−CH$_2$−N), 2.53–2.56 (m, 1H, −C*H*$_2$−CH$_2$−N), 3.99–4.00 (m, 2H, −CH$_2$−C*H*$_2$−N), 5.93–5.95 (m, 1H, C$_6$H$_5$−C*H*−O−), 6.89 (s, 1H, −N−C*H*=CH−N=), 7.03 (s, 1H, −N−CH=C*H*−N=), 7.29–7.46 (m, 6H, −N−C*H*=N−, H$_{ar.}$), 7.38, (d, J = 8.4 Hz, 2H, H$_{ar.}$).7.93 (d, J = 8.4 Hz, 2H, H$_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 37.7 (−*C*H$_2$−CH$_2$−N), 43.5 (−CH$_2$−*C*H$_2$−N), 74.1 (C$_6$H$_5$−*C*−O−), 118.9 (−N−*C*H=CH−N=), 126.4, 128.8, 128.9, 129.0, 129.5, 131.1 (−N−CH=*C*H−N=, CH$_{ar.}$, C$_{ar.}$), 137.1 (−N−*C*H=N−), 139.0, 139.9 (C$_{ar.}$), 164.8 (C=O); MS *m*/*z* (%): 341 (M$^+$, 61), 201 (100); Anal. calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.86; H, 5.10; N, 8.34.

*3-(1H-Imidazol-1-yl)-1-phenylpropyl-2,4-dichlorobenzoate **5c***

Yield 43%; pale yellow viscous oil; IR (KBr): ν (cm^{-1}) 3103, 2942, 1726 (C=O), 1506, 1278, 761; ^{1}H-NMR ($CDCl_3$): δ 2.31–2.35 (m, 1H, −C*H*$_2$−CH$_2$−N), 2.51–2.56 (m, 1H, −C*H*$_2$−CH$_2$−N), 3.98–4.04 (m, 2H, −CH$_2$−C*H*$_2$−N), 5.92–5.93 (m, 1H, C$_6$H$_5$−C*H*−O−), 6.88 (s, 1H, −N−C*H*=CH−N=), 7.02 (s, 1H, −N−CH=C*H*−N=), 7.25–7.44 (m, 8H, −N−C*H*=N−, H$_{ar.}$), 7.72, (dd, J = 8.6, 2.3 Hz, 1H, H$_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 37.6 (−*C*H$_2$−CH$_2$−N), 43.4 (−CH$_2$−*C*H$_2$−N), 74.9 (C$_6$H$_5$−C−O−), 118.8

(–N–*C*H=CH–N=), 126.6, 127.3, 128.0, 128.8, 128.9, 129.8, 131.2, 132.8, 134.9 (–N–CH=*C*H–N=, $CH_{ar.}$, $C_{ar.}$), 137.1 (–N–*C*H=N–), 138.6, 138.8 ($C_{ar.}$), 164.0 (C = O); MS *m/z* (%): 377 (M^++2, 0.6), 375 (M^+, 1), 201 (100), 105 (24), 81 (37); Anal. calcd. for $C_{19}H_{16}Cl_2N_2O_2$: C, 60.81; H, 4.30; N, 7.47. Found: C, 60.73; H, 4.32; N, 7.51.

3-(1H-Imidazol-1-yl)-1-phenylpropyl-4-methoxybenzoate ***5d***

Yield 40%; pale yellow viscous oil; IR (KBr): ν (cm^{-1}) 3114, 2944, 1709 (C=O), 1508, 1263, 763; ^{1}H-NMR ($CDCl_3$): δ 2.30–2.31 (m, 1H, –CH_2–CH_2–N), 2.49–2.50 (m, 1H, –CH_2–CH_2–N), 3.79 (s, 3H, OCH_3), 3.97–3.98 (m, 2H, –CH_2–CH_2–N), 5.89–5.92 (m, 1H, C_6H_5–C*H*–O–), 6.86–7.42 (m, 10H, –N–C*H*=CH–N=, –N–CH=C*H*–N=, –N–C*H*=N–, $H_{ar.}$), 7.95–8.02 (m, 2H, $H_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 37.9 (–*C*H_2–CH_2–N), 43.5 (–CH_2–*C*H_2–N), 55.6 (O*C*H_3), 73.3 (C_6H_5–*C*–O–), 113.9 ($CH_{ar.}$), 118.9 (–N–*C*H=CH–N=), 122.2, 126.3, 128.5, 128.9, 129.5, 131.8, (–N–CH=*C*H–N=, $CH_{ar.}$, $C_{ar.}$), 137.1 (–N–*C*H=N–), 139.6, 163.8 ($C_{ar.}$), 165.4 (C=O); MS *m/z* (%): 336 (M^+, 13), 201 (88), 135 (100), 105 (19), 81 (46); Anal. calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.60; H, 6.01; N, 8.38.

3-(1H-Imidazol-1-yl)-1-phenylpropyl-4-nitrobenzoate ***5e***

Yellowish white solid, yield 70%; mp 138–140°C; IR (KBr): ν (cm^{-1}) 3112, 2960, 1716 (C=O), 1510, 1271, 708; ^{1}H-NMR ($CDCl_3$): δ 2.42–2.43 (m, 1H, –CH_2–CH_2–N), 2.62–2.63 (m, 1H, –CH_2–CH_2–N), 4.02–4.03 (m, 2H, –CH_2–CH_2–N), 5.97–5.98 (m, 1H, C_6H_5–C*H*–O–), 6.91 (s, 1H, –N–C*H*=CH–N=), 7.04 (s, 1H, –N–CH=C*H*–N=), 7.35–7.44 (m, 6H, –N–C*H*=N–, $H_{ar.}$), 8.16, (d, J = 9.2 Hz, 2H, $H_{ar.}$), 8.26 (d, J = 9.2 Hz, 2H, $H_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 37.4 (–*C*H_2–CH_2–N), 43.5 (–CH_2–*C*H_2–N), 75.1 (C_6H_5–*C*–O–), 118.8 (–N–*C*H=CH–N=), 123.7, 126.5, 129.0, 129.1, 129.9, 130.9, 135.2, 137.2 (–N–CH=*C*H–N=, $CH_{ar.}$, $C_{ar.}$), 137.2 (–N–*C*H=N–), 138.5, 150.8 ($C_{ar.}$), 163.9 (C=O); MS *m/z* (%): 351 (M^+, 15), 183 (15), 150 (68) 81 (100); Anal. calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.08; H, 4.79; N, 12.07.

Synthesis of 3-(1H-imidazol-1-yl)-1-phenylpropyl-4-aminobenzoate hydrochloride ***5f***

A solution of 1.0 g (2.8 mmol) of 4-nitro benzoate ester **5e** in THF (20 mL) was hydrogenated at room temperature and normal pressure for 2 h using platinum(IV) oxide 0.06 g (0.28 mmol). The catalyst was filtered off and ethanol was evaporated under reduced pressure to give the corresponding amino derivative as yellow viscous oil which was dissolved in ethyl acetate (5 mL) then acidified with methanolic HCl solution. The acidic mixture was evaporated under reduced pressure to afford the hydrochloride salt **5f** which was recrystallized from ethyl acetate/methanol to afford 0.80 g (80%) of **5f** as a yellowish white crystals, mp 198–202°C; IR (KBr): ν (cm^{-1}) 3416, 2926, 1720 (C=O), 1502, 1270, 764; ^{1}H-NMR (D_2O): δ 2.49–2.50 (m, 1H, –CH_2–CH_2–N), 2.65–2.67 (m, 1H, –CH_2–CH_2–N), 4.65–4.67 (m, 2H, –CH_2–CH_2–N), 5.90–5.92 (m, 1H, C_6H_5–C*H*–O–), 7.20–7.34 (m, 9H, H_{ar}), 7.90 (d, J = 7.05 Hz, 2H, –N–C*H*=C*H*–N=), 8.51 (s, 1H, –N–C*H*=N–); ^{13}C-NMR (D_2O): δ 35.1 (–*C*H_2–CH_2–N), 46.2 (–CH_2–*C*H_2–N), 75.3 (C_6H_5–*C*–O–), 119.9 (–N–*C*H=CH–N=), 120.9, 121.8, 126.1, 126.2, 128.9, 129.1, 131.5, 134.5 (–N–CH=*C*H–N=, $CH_{ar.}$, $C_{ar.}$), 138.8 (–N–*C*H=N–), 140.4, 165.3 ($C_{ar.}$), 166.7 (C=O); MS *m/z* (%): 321 (M^+–HCl, 100), 201 (68), 185 (24), 120 (55); Anal. calcd. for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.68; H, 5.71; N, 11.69.

General procedure for the preparation of the alcohols ***5g–j***

A 250-mL three necked flask was charged with magnesium turnings (0.45 g, 18.5 mmol), diethyl ether (15 mL), and nearly one tenth of the appropriate alkyl, phenyl, or aralkyl halide (15.2 mmol) in diethyl ether (25 mL). The resulting suspension was warmed under stirring prior to initiation of Grignard reaction (few crystals of iodine may be added for initiation). A positive reaction start was detected by initiation of reflux and the remaining alkyl, aryl, or aralkyl halide was then added to the reaction mixture dropwise. Upon completion of the addition, reflux was maintained by heating for 1 h. The ketone **3** (1.0 g, 5.0 mmol) in dry THF (10 mL) was added dropwise to the stirred reaction mixture under reflux. After complete addition of **3**, reflux was continued for 18 h. The reaction mixture was then cooled (0–5°C) and quenched by a slow addition of saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography using chloroform/methanol (9:1) for compound **5g** or recrystallized from ethyl acetate for compounds **5h–j**.

4-(1H-Imidazol-1-yl)-2-phenylbutan-2-ol ***5g***

Yield 71%; pale yellow viscous oil; Anal. IR (KBr): ν (cm^{-1}) 3390 (OH), 2971, 1958, 1674, 1511, 1079, 701; ^{1}H-NMR ($CDCl_3$): δ 1.55 (s, 3H, CH_3), 2.18–2.22 (m, 2H, –CH_2–CH_2–N), 3.64–3.66 (m, 1H, CH_2–N), 4.02–4.03 (m, 1H, CH_2–N), 5.75 (brs., 1H, OH), 6.73 (s, 1H, –N–CH=C*H*–N–), 6.83 (s, 1H, –N–C*H*=CH–N–), 7.31–7.46 (m, 6H, –N–C*H*=N–, $H_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 31.1 (CH_3), 43.1 (–*C*H_2–CH_2–N), 45.4 (–CH_2–*C*H_2–N), 72.9 (CH_3–*C*–OH), 119.2, (–N–*C*H=CH–N=), 124.8, 126.9, 128.4, 128.6, (–N–CH=*C*H–N=, $CH_{ar.}$), 137.4 (–N–*C*H=N–), 147.2 ($C_{ar.}$); MS *m/z* (%): 217 (M^++1, 100), 216 (M^+, 52), 158 (8), 68 (40); Anal. calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.31; H, 7.52; N, 12.86.

4-(1H-Imidazol-1-yl)-1,1-diphenylpropan-1-ol ***5h***

White solid, yield 61%; mp 182–184°C ([5] 165–168°C from ethanol); IR (KBr): ν (cm^{-1}) 3569 (OH), 3112, 1594, 1502, 1450,

753; ^{1}H-NMR ($CDCl_3$): δ 1.80 (brs., 1H, OH), 2.72–2.75 (m, 2H, –C*H*$_2$–CH$_2$–N), 3.89–3.93 (m, 2H, –CH$_2$–C*H*$_2$–N), 6.75 (s, 1H, –N–C*H*=CH–N=), 6.85 (s, 1H, –N–CH=C*H*–N=), 7.26–7.41 (m, 11H, –N–C*H*=N–, H$_{ar.}$); ^{13}C-NMR (DMSO-d_6): δ 42.9 (–*C*H$_2$–CH$_2$–N), 43.2 (–CH$_2$–*C*H$_2$–N), 76.2 (C$_6$H$_5$–*C*–OH), 118.9 (–N–*C*H=CH–N=), 126.1, 126.9, 128.5, 128.9, (–N–CH=*C*H–N=, CH$_{ar.}$), 137.6 (–N–*C*H=N–), 148.0 (C$_{ar.}$); MS *m*/*z* (%): 278 (M$^+$, 22), 183 (53), 105 (100), 67 (74); Anal. calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.59; H, 6.61; N, 10.12.

4-(1H-Imidazol-1-yl)-1,2-diphenylbutan-2-ol ***5i***

White solid, yield 68%; mp 172–174°C; IR (KBr): ν (cm^{-1}) 3177 (OH), 2920, 1594, 1501, 1445, 699; ^{1}H-NMR ($CDCl_3$): δ 2.28–2.30 (m, 1H, –C*H*$_2$–CH$_2$–N), 2.39–2.41 (m, 1H, –C*H*$_2$–CH$_2$–N), 2.69 (brs., 1H, OH), 3.12 (d, J = 13.4 Hz, 1H, –C*H*$_2$–C$_6$H$_5$), 3.19 (d, J = 13.4 Hz, 1H, –C*H*$_2$–C$_6$H$_5$), 3.57–3.59 (m, 1H, –CH$_2$–C*H*$_2$–N), 3.97–3.99 (m, 1H, –CH$_2$–C*H*$_2$–N), 6.75 (s, 1H, –N–C*H*=CH–N=), 6.89–6.92 (m, 2H, H$_{ar.}$), 6.94 (s, 1H, –N–CH=C*H*–N=), 7.18–7.37 (m, 9H, –N–C*H*=N–, H$_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 42.7 (–*C*H$_2$–CH$_2$–N), 43.6 (–CH$_2$–*C*H$_2$–N), 50.3 (*C*H$_2$–C$_6$H$_5$), 76.9 (CH$_2$–*C*–OH), 118.9 (–N–*C*H=CH–N=), 125.3, 127.2, 128.5, 128.6, 129.3, 130.7 (–N–CH=*C*H–N=, CH$_{ar.}$), 135.3 (–N–*C*H=N–), 137.0, 144.3 (C$_{ar}$); MS *m*/*z* (%): 293 (M$^+$ + 1, 28), 292 (M$^+$, 4), 201 (100), 105 (58); Anal. calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.19; H, 6.93; N, 9.67.

1-(1H-Imidazol-1-yl)-3,5-diphenylpentan-3-ol ***5j***

White solid, yield 32%; mp 154–156°C; IR (KBr): ν (cm^{-1}) 3226 (OH), 2930, 1590, 1498, 1447, 698; ^{1}H-NMR ($CDCl_3$): δ 2.17–2.64 (m, 6H, –C*H*$_2$–CH$_2$–N, C$_6$H$_5$–C*H*$_2$–C*H*$_2$–), 3.62–3.64 (m, 1H, –CH$_2$–C*H*$_2$–N), 4.02–4.04 (m, 1H, –CH$_2$–C*H*$_2$–N), 6.77 (s, 1H, –N–C*H*=CH–N=), 7.07 (s, 1H, –N–CH=C*H*–N=), 7.23–7.46 (m, 11H, –N–C*H*=N–, H$_{ar.}$); ^{13}C-NMR ($CDCl_3$): δ 29.9 (C$_6$H$_5$–*C*H$_2$–CH$_2$–), 42.7 (C$_6$H$_5$–CH$_2$–*C*H$_2$–), 44.7 (–*C*H$_2$–CH$_2$–N), 45.5 (–CH$_2$–*C*H$_2$–N), 76.9 (CH$_2$–*C*–OH), 118.9 –N–*C*H=CH–N=), 125.2, 126.0, 127.1, 128.4, 128.6, 128.7 129.0 (–N–CH=*C*H–N=, CH$_{ar.}$), 136.9 (–N–*C*H=N–), 141.9, 144.6 (C$_{ar.}$); MS *m*/*z* (%): 306 (M$^+$, 9), 201 (39), 105 (79), 91 (100); Anal. calcd. for $C_{20}H_{22}N_2O$: C, 78.39; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.33; N, 9.25.

Anti-*Candida* activity

Microorganisms

Candida albicans and *Candida pseudotropicales* as yeast microorganisms were obtained from MIRCEN, Faculty of Agriculture, Ain-Shams University, Cairo, Egypt.

Antimicrobial assay

The synthesized compounds **5a–j** were screened against *Candida albicans* and *Candida pseudotropicales* to evaluate their antimicrobial activities by agar diffusion technique [13]. Sterile nutrient and malt extract agar media will be inoculated, separately, with 100-μL cell suspension of the chosen yeasts and poured into Petri-dishes (20 cm diameter).

The minimum inhibitory concentrations (MICs) of the tested compounds were determined using serial dilutions technique [14]. For each compound, different concentrations ranging from 0.2 to 100.0 μg/mL chloroform were prepared from stock solution (0.1 mg/mL chloroform). Each concentration was placed on filter paper disc (1 cm diameter) in portions (in a successive manner after the preceding portion evaporated). Solvent was allowed to evaporate and the discs were deposited on the surface of inoculated agar plates and kept at low temperature (4°C) for 12 h, before incubation which favors diffusion over microbial growth to detect the inhibition zone clearly.

The plates were incubated at 30°C. Experiments were performed in duplicate and diameters of inhibition zones were measured after 24 h. MIC was expressed as the lowest concentration of the compound that produced complete microbial growth inhibition. Miconazole and tioconazole were used as positive controls. The anti-*Candida* activity was expressed as the diameter of the growth inhibition zone in mm.

Statistical analysis

All antimicrobial results were statistically analyzed using SPSS software, version 14.0. Comparisons between the results of the different compounds were done through analysis of variance (ANOVA) and the post-hoc test, least significant differences (LSD). The significance level was considered at P-value < 0.05.

The authors have declared no conflict of interests.

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