In Vitro Anti-Candida Activity of Certain New 3-(1H-Imidazol-1-yl)propan-1-one Oxime Esters

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Abstract: Anti-Candida activities of certain new oximes 4a–d and their respective aromatic esters 5a–l are reported. The tested compounds 4a–d and 5a–l exhibited better anti-Candida profiles than fluconazole. Compound 5j, namely (E)-3-(1H-imidazol-1-yl)-1-phenylpropan-1-one O-4-chlorobenzoyl oxime emerged as the most active congener, with a MIC value of 0.0054 µmol/mL being more potent than both fluconazole (MIC > 1.6325 µmol/mL) and miconazole (MIC value = 0.0188 µmol/mL) as a new anti-Candida albicans agent.

Keywords: synthesis; Mannich reaction; azoles; oxime esters; anti-Candida

1. Introduction

Fungal infections have recently emerged as a growing threat to human health, especially in patients with weakened or compromised immune systems [1,2]. The organisms most often responsible for invasive fungal infection are Candida and Aspergillus species [3]. Candida infections are adverse in their manifestations, varying from superficial skin problems, chronic infection of the nails, mouth,
throat or vagina to frequently fatal systemic diseases that involve the lungs, heart, gastrointestinal tract, central nervous system and other organs [4]. These infections are considered to be opportunistic in nature, since some aspect of the host’s defense system is impaired in some way. In spite of the large number of the available antifungal agents, the medical need is still largely unmet and therefore, efforts to discover new antifungal agents are a must. This is largely due to the perceived threat of emerging new pathogenic fungi and resistance of many strains to existing therapy [5–7].

Five major classes of the clinically used antifungal drugs are available, namely polyenes (such as amphotericin B and nystatin), echinocandins (such as caspofungin), allylamines (such as naftifine and terbinafine), fluoropyrimidines (such as 5-fluorocytosine) and azoles (such as miconazole, fluconazole and oxiconazole) (Figure 1) [8–10]. Azole antifungal drugs remain the mainstay of therapy for candidal life-threatening fungal infections due to their safety profile and high therapeutic index [11]. The mechanism of action of azole antifungals relies on their ability to inhibit Cyt-P450 dependent sterol 14α-demethylase through binding to the heme cofactor of the cytochrome CYP51 leading to inhibition of sterols synthesis in fungi [4,12].

Figure 1. Azole antifungal agents used in clinical therapy.

An evaluation of the literature exposed that some potent clinically used azole antifungals are derived from oxime-containing scaffolds [13]. Additionally, most of the available imidazole-containing antifungal agents have a two carbon atom spacer between the imidazole pharmacophore and an aromatic moiety, whereas limited information is available about imidazole-containing antifungals having a three-carbon atom linker between the imidazole pharmacophore and the aromatic moiety [14,15]. Moreover, Walker et al. reported that some aryl and aralkyl esters of 2-(1H-imidazol-1-yl)-1-phenylethanols displayed more anti-\textit{Candida albicans} activity than miconazole [16].
Based upon the aforementioned premises, we became interested in the development of new imidazole-containing drug-like anti-Candida agents incorporating oxime functionality, exemplified by compounds 4a–d as well as their respective aromatic esters, compounds 5a–l.

2. Results and Discussion

2.1. Chemistry

The pivotal ketones 3a–d were prepared using the synthetic strategy outlined in Scheme 1. Thus, the appropriate acetophenone 1a–d was reacted with dimethylamine hydrochloride and paraformaldehyde in the presence of a catalytic amount of concentrated hydrochloric acid to yield Mannich base hydrochlorides 2a–d. Imidazole was alkylated with the appropriate Mannich base 2a–d to give ketones 3a–d in good yields (Scheme 1).

Scheme 1. Synthesis of the ketones 3a–d.

| Compound No. | R  |
|--------------|----|
| 1a, 2a, 3a   | H  |
| 1b, 2b, 3b   | 4-Cl |
| 1c, 2c, 3c   | 4-OCH₃ |
| 1d, 2d, 3d   | 4-CH₃ |

Reagents and conditions: (i) HN(CH₃)₂.HCl, (CH₂O), conc. HCl, ethanol, reflux, 2 h; (ii) imidazole, water, reflux, 5 h.

Ketones 3a–d were allowed to react with hydroxylamine hydrochloride in the presence of potassium hydroxide to yield oximes 4a–d. X-ray crystallography is a decisive analytical tool which can confirm the configuration of the produced oximes 4a–d. Accordingly, the assigned (E)-configuration of compounds 4a–d was established via single crystal X-ray structure of the oxime 4a (Figure 2) [17].

The produced oximes 4a–d were subjected to esterification with the appropriate carboxylic acid derivatives using ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl) in the presence of 4-dimethylaminopyridine (DMAP) to yield the target compounds 5a–l (Scheme 2). The chemical structures of oximes 4a–d and the title compounds 5a–l were confirmed via IR, ¹H-NMR, ¹³C-NMR and mass spectral data.
**Figure 2.** ORTEP diagram of the title compound 4a drawn at 50% ellipsoids for non-hydrogen atoms.

**Scheme 2.** Synthesis of the target compounds 5a–l.

| Compound No. | R       | R¹               |
|-------------|---------|------------------|
| 3a, 4a, 5a  | H       | C₆H₅             |
| 3b, 4b, 5b  | 4-Cl    | 4-Cl-C₆H₄        |
| 3c, 4c, 5c  | 4-OCH₃  | 4-Cl-C₆H₄        |
| 3d, 4d, 5d  | 4-CH₃   | 4-Cl-C₆H₄        |
| 5e          | H       | 4-F-C₆H₄         |
| 5f          | H       | 4-CH₂-C₆H₄       |
| 5g          | H       | 4-CF₃-C₆H₄       |
| 5h          | H       | 4-OCH₂-C₆H₄      |
| 5i          | H       | 3,4,5-(OCH₃)₃-C₆H₂ |
| 5j          | H       | 4-Cl-C₆H₄        |
| 5k          | H       | 3-Cl-C₆H₄        |
| 5l          | H       | 2-Cl-C₆H₄        |

Reagents and conditions: (i) H₂NOH-HCl, KOH, ethanol, reflux, 18 h.; (ii) an appropriate carboxylic acid, EDCI-HCl, DMAP, DCM, rt, 18 h.

2.2. In Vitro Anti-Candida Activity and SARs

Fluconazole is the gold standard azole antifungal and used clinically as the first line of treatment for fungal infections, especially those caused by *C. albicans*. However, its extensive medical use has led to
the emergence of resistance [18]. The *in vitro* anti-*Candida* activity of the synthesized imidazole-containing oximes 4a–d and their respective aromatic esters 5a–l was evaluated against two clinical isolates of *Candida, C. albicans* and *C. tropicalis*, which are resistant to fluconazole (MIC > 1.6325 µmol/mL). The test compounds 4a–d and 5a–l incorporate a three-carbon atom bridge between the imidazole pharmacophore and the aromatic moiety to gain insight about anti-*Candida* activity of this type of compounds. The anti-*Candida* activities, expressed as diameter of the inhibition zone (DIZ) and minimum inhibition concentration (MIC) for the oximes 4a–d, the target compounds 5a–l as well as for the reference drugs fluconazole and miconazole, are summarized in Table 1.

**Table 1.** Anti-*Candida* activity of oximes 4a–d and the target compounds 5a–l against *Candida albicans* and *Candida tropicalis*.

| Compound No | *Candida albicans* | *Candida tropicalis* |
|-------------|---------------------|----------------------|
|             | DIZ ± SD * | MIC (µmol/mL) ** | DIZ ± SD * | MIC (µmol/mL) ** |
| 4a          | 21 ± 1.0    | 0.5807              | 20 ± 0.5    | 0.5807            |
| 4b          | 13 ± 0.6    | 0.5019              | 8 ± 1.0     | 0.5019             |
| 4c          | 9 ± 1.15    | 0.5099              | 8 ± 1.0     | 0.2549             |
| 4d          | 8 ± 1.0     | 0.5456              | 8 ± 1.0     | 0.5456             |
| 5a          | 11 ± 1.2    | 0.3919              | 8 ± 1.0     | 0.7837             |
| 5b          | 18 ± 1.1    | 0.0805              | 12 ± 1.0    | 0.6439             |
| 5c          | 16 ± 0.4    | 0.3257              | 16 ± 1.2    | 0.3257             |
| 5d          | 18 ± 0.9    | 0.1699              | 14 ± 0.5    | 0.3398             |
| 5e          | 16 ± 0.9    | 0.3708              | 14 ± 0.6    | 0.3708             |
| 5f          | 7 ± 1.0     | 0.3752              | 8 ± 1.0     | 0.1876             |
| 5g          | 13 ± 0.6    | 0.6454              | 14 ± 1.0    | 0.3227             |
| 5h          | 24 ± 1.1    | 0.0112              | 17 ± 1.0    | 0.3582             |
| 5i          | 17 ± 1.1    | 0.3053              | 14 ± 0.5    | 0.3053             |
| 5j          | 25 ± 1.0    | 0.0054              | 25 ± 1.2    | 0.1767             |
| 5k          | 20 ± 0.9    | 0.0221              | 14 ± 0.5    | 0.7069             |
| 5l          | 12 ± 1.0    | 0.7069              | 12 ± 0.7    | 0.3535             |
| Fluconazole | 15 ± 0.5    | >1.6325             | 16 ± 0.5    | >1.6325            |
| Miconazole  | 38 ± 1.1    | 0.0188              | 24 ± 0.5    | 0.0024             |

* The arithmetic mean of the inhibition zone diameters in mean ± standard deviation in mm. ** The lowest concentration of the compound that produced 80% microbial growth inhibition (µmol/mL).

The preliminary anti-*Candida* potential of the test compounds 4a–d and 5a–l was evaluated using the DIZ assay and the results are presented in Table 1. The test compounds displayed a promising anti-*Candida* activity (DIZ = 7–25 mm) where compound 5j was the most active congener (DIZ = 25 ± 1 and 25 ± 1.2 mm against *C. albicans* and *C. tropicalis*, respectively).

The oxime 4a exhibited good anti-*Candida* activity (MIC value = 0.5807 µmol/mL) toward both *C. albicans* and *C. tropicalis*, being more potent than fluconazole (MIC value > 1.6325 µmol/mL) but weaker than miconazole (MIC value = 0.0188 and 0.0024 µmol/mL for *C. albicans* and *C. tropicalis*, respectively). Substitution of the aromatic ring of 4a with substituents endowed with different electronic and steric properties like chloro, methoxy and/or methyl groups gave compounds 4b, 4c and 4d,
respectively, aiming to enhance its anti-Candida activity. Unfortunately, the anti-Candida activity of 4a did not improve significantly, except for compound 4c toward C. tropicalis (MIC value = 0.2549 µmol/mL).

De Vita et al. reported that the presence of a second aromatic ring could enhance the antifungal activity of azoles [19]. Consequently, the respective aromatic esters 5a–l of the oximes 4a–d were prepared and biologically evaluated as new anti-Candida agents. Esterification of the hydroxyl group of 4a with benzoic acid gave compound 5a which displayed better anti-Candida activity (MIC value = 0.3919 µmol/mL) than that of 4a toward C. albicans. Moreover, esterification of the hydroxyl group of the oximes 4b–d with 4-chlorobenzoic acid gave the respective esters 5b–d. Compounds 5b–d showed better anti-Candida profile than their respective oximes 4b–d, where compound 5b is the most active congener with a MIC value of 0.0805 µmol/mL toward C. albicans.

Substitution of the aromatic ester functionality of 5a with fluoride, methyl and/or trifluoromethyl groups gave compounds 5e–g which exhibited anti-Candida albicans activity comparable with that of 5a, except for compound 5g (MIC value = 0.6454 µmol/mL) which was weaker than 5a. Compounds 5e–g displayed better anti-Candida tropicalis profiles than that of 5a where compound 5f is the most active candidate with a MIC value of 0.1876 µmol/mL.

Substitution of the aromatic ester functionality of 5a with a group endowed with negative inductive effect and positive mesomeric properties like a methoxy group gave compound 5h, which showed a comparable anti-Candida albicans profile (MIC value = 0.0112 µmol/mL) with that of miconazole (MIC value = 0.0188 µmol/mL) and was about 145-fold more potent than fluconazole (MIC > 1.6325 µmol/mL). This result encouraged us to synthesize the trimethoxy analogue of 5a, compound 5i. Unfortunately, 5i exhibited weaker anti-Candida albicans (MIC value = 0.3053 µmol/mL) than that of 5h.

Compound 5j emerged as the most active congener in the whole series of synthesized compounds against both C. albicans and C. tropicalis. Compound 5j, the 4-chloro analogue of 5a, exhibited about 3.5-fold and 300-fold more potency than miconazole and the gold standardazole antifungal, fluconazole, respectively, as a drug-like anti-Candida albicans agent. The positional isomers of compound 5j, compounds 5k and 5l, displayed weaker anti-Candida activity than that of 5j.

3. Experimental

3.1. Chemistry

3.1.1. General

Melting points were determined on a Gallenkamp melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR spectra were carried out on a Bruker NMR spectrometer operating at 500 MHz for 1H and 125.76 MHz for 13C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. TMS was used as internal standard and chemical shift values were recorded in ppm on δ scale. The 1H-NMR data were represented as follows: chemical shifts, multiplicity (s. singlet, d. doublet, t. triplet, m. multiplet, br. broad) and number of protons. The 13C-NMR data were represented as chemical shifts and type of carbon. Mass spectra were measured on Agilent Triple Quadrupole 6410 QQQ LC/MS with an electrospray ionization (ESI) source. Silica gel thin layer chromatography (TLC) plates from Merck (silica gel precoated aluminium plates with a 245 nm fluorescent indicator) 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 and chloroform/methanol (9:0.5) was used as a solvent system.

3.1.2. General Procedure for Preparation of the Ketones 3a–d

The appropriate acetophenone 1a–d (200 mmol), dimethylamine hydrochloride (270 mmol) and paraformaldehyde (90 mmol) were heated to reflux in absolute ethanol (35 mL) in the presence of catalytic amount of concentrated hydrochloric acid (0.5 mL). Reflux of the reaction mixture was continued under stirring for two hours, cooled and acetone (200 mL) was added. The formed Mannich base hydrochlorides 2a–d were precipitated, filtered off and dried. Subsequently, compounds 2a–d (100 mmol) were dissolved in water (100 mL) and imidazole (200 mmol) was added. The reaction mixture was heated to reflux for five hours, cooled and the precipitated solids were collected by filtration to give ketones 3a–d which were pure enough to be used in the next step.

3-(1H-Imidazol-1-yl)-1-phenylpropan-1-one (3a). Synthesis of 3a was previously reported [14].

1-(4-Chlorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (3b). Synthesis of 3b was previously reported [15].

3-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)propan-1-one (3c). Synthesis of 3c was previously reported [20].

3-(1H-Imidazol-1-yl)-1-(4-methylphenyl)propan-1-one (3d). Synthesis of 3d was previously reported [21].

3.1.3. General Procedure for Preparation of the Oximes 4a–d

A mixture of the appropriate ketone 3a–d (10 mmol), hydroxylamine hydrochloride (20 mmol), and KOH (20 mmol) in ethanol (10 mL) was heated to reflux under stirring for 18 h. The reaction mixture was allowed to cool to room temperature and the insoluble solids were filtered off. The filtrate was concentrated under vacuum and the residue was poured onto ice-cold water (15 mL). The precipitated solids were collected by filtration and dried to give oximes 4a–d which were subsequently subjected to the esterification step without any further purification.

(1E)-N-Hydroxy-3-(1H-imidazol-1-yl)-1-phenylpropan-1-imine (4a). [17] Yield 70%; colourless solid mp. 155–157 °C (ethanol); IR (KBr): ν (cm⁻¹) 3508 (OH), 3149, 3002, 2703, 1644 (C=N), 1600, 1573, 1221, 758; ¹H-NMR (CDCl₃): δ 3.31 (t, J = 7.1 Hz, 2H, -CH₂-CH₂-N), 4.28 (t, J = 7.1 Hz, 2H, -CH₂-CH₂-N), 6.96 (s, 1H, -N-CH=CH=N=), 7.07 (s, 1H, -N-CH=CH=N=), 7.29–7.49 (m 5H, Ar-H), 7.58 (s, 1H, -N-CH=N-); ¹³C-NMR (CDCl₃): δ 28.3 (-CH₂-CH₂-N), 41.8 (-CH₂-CH₂-N), 119.1 (-N=CH=CH-N=), 126.1, 128.8, 128.9 (-N-CH=CH=N=, Ar-CH), 135.1, 137.0 (Ar-C), 139.5 (-N-CH=N-), 155.4 (C=N-OH); MS m/z (ESI): 216.0 [M + 1]⁺.

(1E)-1-(4-Chlorophenyl)-N-hydroxy-3-(1H-imidazol-1-yl)propan-1-imine (4b). The synthesis and characterization of 4b were previously reported [22].
(1E)-N-Hydroxy-3-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)propan-1-imine (4c). Yield 65%; pale yellow solid mp. 136–138 °C (ethanol); IR (KBr): \( \nu (\text{cm}^{-1}) \) 3512 (OH), 3135, 3026, 2632, 1648 (C=N), 1680, 1566, 1228, 752; \(^1\)H-NMR (CDCl\(_3\)): \( \delta \) 3.26 (t, \( J = 6.5 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 3.83 (s, 3H, -N-CH=CH-N), 4.28 (t, \( J = 7.1 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 6.89 (d, \( J = 7.5 \) Hz, 2H, Ar-H), 6.97 (s, 1H, -N-CH=CH-N), 7.08 (s, 1H, -N-CH=CH-N), 7.44 (d, \( J = 7.5 \) Hz, 2H, Ar-H), 7.58 (s, 1H, -N-CH=CH-N); \(^{13}\)C-NMR (CDCl\(_3\)): \( \delta \) 28.9 (-C\(_H_2\)-CH\(_2\)-N), 43.6 (-CH\(_2\)-C\(_H_2\)-N), 55.4 (OCH\(_3\)), 114.0 (Ar-CH), 119.1 (-N-CH=CH-N), 127.4, 127.9, 129.1 (-N-CH=CH-N), 137.1 (-N-CH=CH-N), 155.4 (C=O-CH\(_3\)); MS \( m/z \) (ESI): 246.0 [M + 1]+.

(1E)-N-Hydroxy-3-(1H-imidazol-1-yl)-1-(4-methylphenyl)propan-1-imine (4d). Yield 65%; white solid mp. 147–149 °C (ethanol); IR (KBr): \( \nu (\text{cm}^{-1}) \) 3509 (OH), 3119, 2702, 1639 (C=N), 1679, 1512, 1230, 738; \(^1\)H-NMR (CDCl\(_3\)): \( \delta \) (ppm) = 2.27 (s, 3H, CH\(_3\)), 3.18 (t, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 4.18 (t, \( J = 7.0 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 6.88 (s, 1H, -N-CH=CH-N), 6.99 (s, 1H, -N-CH=CH-N), 7.08 (d, \( J = 7.8 \) Hz, 2H, Ar-H), 7.30 (d, \( J = 7.9 \) Hz, 2H, Ar-H), 7.49 (s, 1H, -N-CH=CH-N); \(^{13}\)C-NMR (CDCl\(_3\)): \( \delta \) 21.3 (CH\(_3\)), 28.9 (-C\(_H_2\)-CH\(_2\)-N), 43.6 (-CH\(_2\)-C\(_H_2\)-N), 119.1 (-N-CH=CH-N), 125.9, 129.1, 129.4 (-N-CH=CH-N), 132.6, 137.1, 139.4 (-N-CH=CH-N), 154.7 (C=O-CH\(_3\)); MS \( m/z \) (ESI): 230.0 [M + 1]+.

3.1.4. General Procedure for the Synthesis of the Target Oxime Esters 5a–l

A solution of the appropriate carboxylic acid (7 mmol) and EDCI·HCl (7.3 mmol) was stirred in DCM (75 mL) in the presence of DMAP (400 mg). The appropriate oxime 4a–d (6.9 mmol) was added to the stirred reaction mixture and stirring was continued for further 18 h at room temperature. The reaction mixture was washed successively with water (2 × 20 mL), 10% NaHCO\(_3\) solution (2 × 15 mL), and water (2 × 15 mL). The organic layer was separated, dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure and the residue was purified either by recrystallisation (for solids) or by column chromatography (for oils).

(E)-3-(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-benzoyl oxime (5a). Yield 41%; colourless viscous oil; IR (KBr): \( \nu (\text{cm}^{-1}) \) 3115, 2943, 1746 (C=O), 1650 (C=N), 1510, 1243, 735; \(^1\)H-NMR (CDCl\(_3\)): \( \delta \) 3.38 (t, \( J = 7.1 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 4.21 (t, \( J = 7.1 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 6.84 (s, 1H, -N-CH=CH-N), 6.95 (s, 1H, -N-CH=CH-N), 7.36-7.46 (m, 6H, -N-CH=CH-N, Ar-H), 7.55-7.60 (m, 2H, Ar-H), 7.96 (d, \( J = 7.6 \) Hz, 2H, Ar-H); \(^{13}\)C-NMR (CDCl\(_3\)): \( \delta \) 31.0 (-C\(_H_2\)-CH\(_2\)-N), 43.7 (-CH\(_2\)-CH\(_2\)-N), 118.8 (-N-CH=CH-N), 127.3, 128.6, 128.8, 129.1, 129.6, 130.0, 131.3 (-N-CH=CH-N, Ar-CH, Ar-C), 133.0, 133.8, 136.9 (-N-CH=CH-N, Ar-CH, Ar-C), 163.4 (C=O); MS \( m/z \) (ESI): 320.1 [M + 1]+.

(E)-1-(4-Chlorophenyl)-3-(1H-imidazol-1-yl)propan-1-one O-4-chlorobenzoyl oxime (5b). Yield 56%; white solid mp. 132–134 °C (isopropanol); IR (KBr): \( \nu (\text{cm}^{-1}) \) 3107, 1744 (C=O), 1650 (C=N), 1510, 1243, 735; \(^1\)H-NMR (CDCl\(_3\)): \( \delta \) (ppm) = 3.38 (t, \( J = 7.1 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 4.21 (t, \( J = 7.1 \) Hz, 2H, -CH\(_2\)-CH\(_2\)-N), 6.84 (s, 1H, -N-CH=CH-N), 6.95 (s, 1H, -N-CH=CH-N), 7.36-7.46 (m, 6H, -N-CH=CH-N, Ar-H), 7.55-7.60 (m, 2H, Ar-H), 7.96 (d, \( J = 7.6 \) Hz, 2H, Ar-H); \(^{13}\)C-NMR (CDCl\(_3\)): \( \delta \) 31.0 (-CH\(_2\)-CH\(_2\)-N), 43.7 (-CH\(_2\)-CH\(_2\)-N), 118.8 (-N-CH=CH-N), 127.3, 128.6, 128.8, 129.1, 129.6, 130.0, 131.3 (-N-CH=CH-N, Ar-CH, Ar-C), 133.0, 133.8, 136.9 (-N-CH=CH-N, Ar-CH, Ar-C), 163.4 (C=O); MS \( m/z \) (ESI): 320.1 [M + 1]+.
126.9, 128.5, 129.2, 129.4, 130.0, 130.9, 131.2, (-N-CH=CH-N=, Ar-CH, Ar-C), 136.9, 137.8, 140.4 (-N-CH=CH-N=, Ar-C), 162.5 (C=N), 162.6 (C=O); MS m/z (ESI): 388.0 [M^+].

(E)-3-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)propan-1-one O-4-chlorobenzoyl oxime (5c). Yield 70%; white solid mp. 131–133 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3123, 2366, 1758 (C=O), 1684 (C=N), 1564, 1514, 1252, 747; ^1H-NMR (CDCl₃): δ (ppm) = 3.44 (t, J = 6.9 Hz, 2H, -CH₂CH₂-N), 3.87 (OC₃H₃), 4.32 (t, J = 7.0 Hz, 2H, -CH₂CH₂-N), 6.92 (s, 1H, -N-CH=CH-N=), 6.96 (d, J = 8.8 Hz, 2H, Ar-H), 7.09 (s, 1H, -N-CH=CH-N=), 7.49 (d, J = 8.6 Hz, 2H, Ar-H), 7.67 (d, J = 9.0 Hz, 2H, Ar-H), 7.77 (s, 1H, -N-CH=CH-N=), 7.94 (d, J = 8.6 Hz, 2H, Ar-H); ^13C-NMR (CDCl₃): δ 30.5 (-C=H₂CH₂-N), 44.2 (-CH₂CH₂-N), 55.5 (OCH₃), 114.5 (Ar-CH), 119.1 (-N-CH=CH-N=), 128.5, 128.9, 129.2, 130.9, 131.2, (-N-CH=CH-N=, Ar-CH, Ar-C), 136.8, 140.2 (-N-CH=CH-N=, Ar-C), 162.3, 162.8, 162.9 (C=N, C=O, Ar-C); MS m/z (ESI): 384.2 [M + 1]^+.

(E)-3-(1H-Imidazol-1-yl)-1-(4-methylphenyl)propan-1-one O-4-chlorobenzoyl oxime (5d). Yield 58%; white solid mp. 142–144 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3065, 1744 (C=O), 1654 (C=N), 1559, 1508, 1254, 749; ^1H-NMR (CDCl₃): δ (ppm) = 2.42 (s, 3H, CH₃), 3.46 (t, J = 7.0 Hz, 2H, -CH₂CH₂-N), 4.31 (t, J = 6.9 Hz, 2H, -CH₂CH₂-N), 6.91 (s, 1H, -N-CH=CH-N=), 7.09 (s, 1H, -N-CH=CH-N=), 7.27 (d, J = 7.9 Hz, 2H, Ar-H), 7.49 (d, J = 8.5 Hz, 2H, Ar-H), 7.62 (d, J = 8.0 Hz, 2H, Ar-H), 7.79 (s, 1H, -N-CH=CH-N=), 7.94 (d, J = 8.5 Hz, 2H, Ar-H); ^13C-NMR (CDCl₃): δ 21.5 (CH₃), 30.6 (-CH₂CH₂-N), 44.2 (-CH₂CH₂-N), 119.1 (-N-CH=CH-N=), 127.2, 128.4, 128.5, 129.2, 129.9, 130.9, 131.2, (-N-CH=CH-N=, Ar-CH, Ar-C), 136.8, 140.2, 142.1 (-N-CH=CH-N=, Ar-C), 162.7 (C=N), 163.3 (C=O); MS m/z (ESI): 368.2 [M + 1]^+.

(E)-3-(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-4-fluorobenzoyl oxime (5e). Yield 62%; pale yellow solid mp. 114–116 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3115, 2848, 1746 (C=O), 1660 (C=N), 1571, 1249, 739; ^1H-NMR (CDCl₃): δ (ppm) = 3.46 (t, J = 7.0 Hz, 2H, -CH₂CH₂-N), 4.29 (t, J = 7.0 Hz, 2H, -CH₂CH₂-N), 6.91 (s, 1H, -N-CH=CH-N=), 7.02 (s, 1H, -N-CH=CH-N=), 7.18–7.21 (m, 2H, Ar-H), 7.43–7.52 (m, 4H, -N-CH=CH-N=, Ar-H), 7.68 (d, J = 7.4 Hz, 2H, Ar-H), 8.03–8.05 (m, 2H, Ar-H); ^13C-NMR (CDCl₃): δ 30.9 (-C=H₂CH₂-N), 43.8 (-CH₂CH₂-N), 116.1 (d, J = 22.1 Hz, Ar-CH), 118.8 (-N-CH=CH-N=), 124.9, (d, J = 2.6 Hz, Ar-C), 127.3, 129.1, 129.8, 131.4 (-N-CH=CH-N=, Ar-CH), 132.2 (d, J = 9.4 Hz, Ar-CH), 132.8, 136.9 (-N-CH=CH-N=, Ar-C), 162.5 (C=N), 163.5 (C=O), 167.1 (d, J = 254.0 Hz, Ar-C); MS m/z (ESI): 338.2 [M + 1]^+.

(E)-3-(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-4-methylbenzoyl oxime (5f). Yield 62%; pale yellow solid mp. 125–127 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3115, 2964, 1736 (C=O), 1660 (C=N), 1605, 1506, 1248, 750; ^1H-NMR (CDCl₃): δ (ppm) = 2.37 (s, 3H, CH₃), 3.36 (t, 2H, J = 7.1 Hz, -CH₂CH₂-N), 4.21 (t, 2H, J = 7.0 Hz -CH₂CH₂-N), 6.84 (s, 1H, -N-CH=CH-N=), 6.94 (s, 1H, -N-CH=CH-N=), 7.23 (d, J = 7.8 Hz, 2H, Ar-H), 7.35–7.41 (m, 4H, -N-CH=CH-N=, Ar-H), 7.59 (d, J = 7.0 Hz, 2H, Ar-H), 7.85 (d, J = 8.0 Hz, 2H, Ar-H); ^13C-NMR (CDCl₃): δ 21.8 (CH₃), 31.1 (-CH₂CH₂-N), 43.7 (-CH₂CH₂-N), 118.8 (-N-CH=CH-N=), 125.8, 127.2, 129.0, 129.5, 129.6, 130.1, 131.2, 133.1 (-N-CH=CH-N=, Ar-CH, Ar-C), 136.9 (-N-CH=CH-N=), 144.7 (Ar-C), 163.2 (C=N), 163.5 (C=O); MS m/z (ESI): 334.0 [M + 1]^+.
(E)-3-[(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-4-(trifluoromethyl)benzoyl oxime (5g). Yield 39%; white solid mp. 125–127 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3050, 2360, 1750 (C=O), 1653 (C=N), 1559, 1507, 1264, 737;¹H-NMR (CDCl₃): δ (ppm) = 3.47–3.49 (m, 2H, -CH₂-CH₂-N), 4.29–4.32 (m, 2H, -CH₂-CH₂-N), 6.91 (s, 1H, -N=CH=CH-N=), 7.05 (s, 1H, -N=CH=CH-N=), 7.36–7.55 (m, 4H, -N=CH=CH-N, Ar-H), 7.71–7.72 (m, 2H, Ar-H), 7.79 (d, J = 8.0 Hz, 2H, Ar-H), 8.13 (d, J = 8.0 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ 30.8 (-CH₂-CH₂-N), 43.8 (-CH₂-CH₂-N), 118.8 (-N=CH=CH-N=), 125.8 (d, J = 3.4 Hz, CF₃), 125.9, 127.3, 128.6, 129.2, 129.8, 130.0, 131.6, 132.6 (-N=CH=CH-N=, Ar-CH, Ar-C), 135.6, 136.9 (-N=CH=CH-N=, Ar-C), 162.4 (C=N), 164.0 (C=O); MS m/z (ESI): 388.1 [M + 1]⁺.

(E)-3-[(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-4-methoxybenzoyl oxime (5h). Yield 40%; off white solid mp. 108–110 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3117, 2968, 1735 (C=O), 1650 (C=N), 1602, 1507, 1248, 765;¹H-NMR (CDCl₃): δ (ppm) = 3.46 (t, J = 6.9 Hz, 2H, -CH₂-CH₂-N), 3.91 (s, 3H, OCH₃), 4.30 (t, J = 6.9 Hz, 2H, -CH₂-CH₂-N), 6.94 (s, 1H, -N=CH=CH-N=), 7.01 (d, J = 8.8 Hz, 2H, Ar-H), 7.10 (s, 1H, -N=CH=CH-N=), 7.45–7.50 (m, 4H, -N=CH=CH-N-, Ar-H), 7.67 (d, J = 7.0 Hz, 2H, Ar-H), 8.01 (d, J = 8.8 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ 31.0 (-CH₂-CH₂-N), 43.7 (-CH₂-CH₂-N), 55.6 (OCH₃), 114.1 (Ar-CH), 118.8 (-N=CH=CH-N=), 120.7, 127.2, 129.0, 130.0, 131.2, 131.7, 133.1 (-N=CH=CH-N=, Ar-CH, Ar-C), 136.9 (-N=CH=CH-N=), 162.9 (C=N), 163.2 (Ar-C), 164.0 (C=O); MS m/z (ESI): 350.0 [M + 1]⁺.

(E)-3-[(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-3,4,5-trimethoxybenzoyl oxime (5i). Yield 53%; white solid mp. 135–137 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3103, 2938, 1742 (C=O), 1645 (C=N), 1593, 1503, 1231, 749;¹H-NMR (CDCl₃): δ (ppm) = 3.45 (t, J = 6.8 Hz, 2H, -CH₂-CH₂-N), 3.92 (s, 6H, 2 × OCH₃), 3.94 (s, 3H, OCH₃), 4.28 (t, J = 6.8 Hz, 2H, -CH₂-CH₂-N), 6.91 (s, 1H, -N=CH=CH-N=), 7.02 (s, 1H, -N=CH=CH-N=), 7.27–7.50 (m, 6H, -N=CH=CH-N-, Ar-H), 7.67 (d, J = 7.0 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ 30.9 (-CH₂-CH₂-N), 43.6 (-CH₂-CH₂-N), 56.5 (2 × OCH₃), 61.0 (OCH₃), 106.9 (Ar-CH), 118.6 (-N=CH=CH-N=), 123.5, 127.3, 129.1, 130.1, 131.3, 132.9 (-N=CH=CH-N=, Ar-CH, Ar-C), 136.8 (-N=CH=CH-N=), 142.9, 153.2 (Ar-C), 163.2 (C=N), 163.6 (C=O); MS m/z (ESI): 410.1 [M + 1]⁺.

(E)-3-[(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-4-chlorobenzoyl oxime (5j). Yield 54%; colourless crystals mp. 126–128 °C (isopropanol); IR (KBr): ν (cm⁻¹) 3115, 2970, 1743 (C=O), 1648 (C=N), 1508, 1249, 736;¹H-NMR (CDCl₃): δ (ppm) = 3.44 (t, J = 6.7 Hz, 2H, -CH₂-CH₂-N), 4.27 (t, J = 6.7 Hz, 2H, -CH₂-CH₂-N), 6.90 (s, 1H, -N=CH=CH-N=), 7.02 (s, 1H, -N=CH=CH-N=), 7.45–7.50 (m, 6H, -N=CH=CH-N-, Ar-H), 7.68 (d, J = 8.4 Hz, 2H, Ar-H), 7.95 (d, J = 8.4 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ 30.9 (-CH₂-CH₂-N), 43.7 (-CH₂-CH₂-N), 118.7 (-N=CH=CH-N=), 127.1, 127.3, 129.1, 129.2, 130.1, 130.9, 131.4, 132.8 (-N=CH=CH-N=, Ar-CH, Ar-C), 136.9 (-N=CH=CH-N=), 140.2 (Ar-C), 162.7 (C=N), 163.7 (C=O); MS m/z (ESI): 354.1 [M + 1]⁺.

(E)-3-[(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-3-chlorobenzoyl oxime (5k). Yield 61%; pale yellow viscous oil; IR (KBr): ν (cm⁻¹) 3113, 1751 (C=O), 1654 (C=N), 1510, 1282, 739;¹H-NMR (DMSO-d₆): δ (ppm) = 3.52 (br. s, 2H, -CH₂-CH₂-N), 4.30 (br. s, 2H, -CH₂-CH₂-N), 6.80 (s, 1H, -N=CH=CH-N=), 7.17 (s, 1H, -N=CH=CH-N=), 7.51–7.82 (m, 8H, -N=CH=CH-N-, Ar-H), 8.00 (d, J = 1.5 Hz, 2H, Ar-H); ¹³C-NMR (DMSO-d₆): δ 30.1 (-CH₂-CH₂-N), 43.0 (-CH₂-CH₂-N), 119.3 (-N=CH=CH-N=),
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127.3, 128.1, 128.5, 128.9, 130.3, 130.9, 131.1, 132.9, 133.6, 133.7 (-N-CH=CH-N=, Ar-CH, Ar-C), 137.1 (-N-CH=N-), 161.7 (C=N), 164.8 (C=O); MS m/z (ESI): 354.1 [M]+.

(E)-3-(1H-Imidazol-1-yl)-1-phenylpropan-1-one O-2-chlorobenzoyl oxime (5l). Yield 60%; white solid mp. 118–120 °C (isopropanol); IR (KBr): ν (cm\(^{-1}\)) 3054, 1763 (C=O), 1658 (C=N), 1640, 1511, 1265, 739; \(^1\)H-NMR (DMSO-d\(_6\)): δ (ppm) = 3.45 (br. s, 2H, -CH\(_2\)-CH-N), 4.25 (br. s, 2H, -CH\(_2\)-N), 6.80 (s, 1H, -N-CH=CH-N=), 7.08 (s, 1H, -N-CH=CH-N=), 7.51-7.67 (m, 7H, -N-C=H-N-, Ar-H), 7.75 (d, J = 6.9 Hz, 2H, Ar-H), 7.90 (d, J = 7.2 Hz, 1H, Ar-H); \(^1^3\)C-NMR (DMSO-d\(_6\)): δ 30.2 (-CH\(_2\)-CH-N), 43.0 (-CH\(_2\)-N), 119.2 (-N-CH=CH-N=), 127.3, 127.6, 128.5, 128.8, 129.9, 130.9, 131.1, 131.3, 131.9, 132.8, 133.7 (-N-CH=CH-N=, Ar-CH, Ar-C), 137.1 (-N-CH=N-), 162.2 (C=N), 164.6 (C=O); MS m/z (ESI): 354.1 [M]+.

3.2. Anti-Candida Activity

3.2.1. Anti-Candida Agents

Miconazole was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA) and fluconazole from Shouguang-Fukang Pharmaceutical Ltd. (Shandong, China). The antifungal discs (containing 25 µg fluconazole and/or 10 µg miconazole) were purchased from ROSCO (Neo-Sensitabs, Taastrup, Denmark). Dimethyl sulfoxide (100%) was used to dissolve stock solutions of miconazole, fluconazole and/or the synthesized compounds 4a–d and 5a–l to obtain an initial concentration of 1000 µg/mL. These stock solutions were then diluted to the desired concentration with sterile distilled water. Miconazole and fluconazole antifungal discs were stored at –80 °C until used.

3.2.2. Media

Liquid RPMI 1640 medium supplemented with L-glutamine was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA) and was added to 2% sodium bicarbonate and 0.165 M morpholine- propane sulfonic acid (MOPS) from Dojindo Laboratories (Kumamoto, Japan) then adjusted to pH 7.0. Sabouraud Dextrose Agar (SDA) and Brain Heart Infusion Broth (BHI) from Difco Laboratories (Detroit, MI, USA). Potato dextrose agar (PDA) was purchased from Eiken Chemical Co. Ltd. (Tokyo, Japan).

3.2.3. Organisms

Two clinical isolates of Candida species were obtained from King Khaled Hospital, Riyadh, Saudi Arabia. One was identified as C. albicans and the other as C. tropicalis. The yeasts were stored at –70 °C in BHI with glycerol 5% until tested.

3.2.4. Preparation of Inocula

Preparation of inocula for the broth microdilution testing was performed in accordance with CLSI documents M27-A2 [23] with RPMI 1640 medium. Yeast isolates were subcultured at 35 °C for 48 h on PDA plates. Candida cells were then recovered and suspended in 5 mL of sterile saline. The turbidity of each suspension was adjusted to a 0.5 McFarland standard (corresponding to 1–3 × 10\(^6\) to 5–3 × 10\(^6\) CFU/mL) at a wavelength of 530 nm according to the reported method [23]. Each
suspension was diluted 1,000-fold with sterile RPMI 1640 medium to give a final inoculum of 1–3 × 10³ to 5–3 × 10³ CFU/mL.

3.2.5. Disk Diffusion Assay

The disk diffusion assay was performed as described previously [24]. Colonies obtained from the Candida strains under test were suspended in sterile saline and adjusted to a 0.5 McFarland standard (corresponding to 5 × 10⁶ CFU/mL). An aliquot of 100 μL of each yeast suspension was spread uniformly onto SDA plates. Six mm Whatmann filter paper disks were impregnated with 1000 μg of the synthesized compounds 4a–d and 5a–l and were allowed to dry. Then they were placed onto the surface of the inoculated agar plates together with the standard antifungal discs which were then incubated at 35 °C. Diameters of inhibition zones were measured at 24 h.

3.2.6. Antifungal Susceptibility Studies

The MIC of the reference standards and/or the synthesized compounds 4a–d and 5a–l were determined with a microdilution test (M27-A2 Protocol), according to the reference method of the CLSI. The previously prepared yeast inocula (100 μL) were added to each well of 96-well flat-bottom microdilution plates; each well contained 100 μL of twofold serial dilutions of the standard or the synthesized compounds 4a–d and 5a–l ranging from 1 μg/mL to 500 μg/mL in RPMI 1640 medium. Readings were measured at 490 nm with a microplate ELISA reader after each plate was incubated at 35 °C for 48 h. The MICs for the reference standards and/or the synthesized compounds were determined with 80% growth inhibition at the end point relative to the turbidity of the growth control.

4. Conclusions

Anti-Candida activities of certain new imidazole-containing oximes 4a–d and their respective aromatic esters 5a–l have been reported. The synthesized compounds 4a–d and 5a–l exhibited anti-Candida activity better than that of the gold standard antifungal drug, fluconazole. Compound 5j emerged as the most active congener among the all synthesized compounds, being about 3.5-fold and 300-fold more potent than miconazole and fluconazole, respectively. Compound 5j could be considered as a prodrug and could serve as a new lead for anti-Candida agents.

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Conflicts of Interests

The authors have declared that there is no conflict of interests.
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*Sample Availability*: Contact the authors.

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