(*E*)-3-(1*H*-Imidazol-1-yl)-1-phenylpropan-1-one *O*-2-chlorobenzoyl oxime: synthesis, single crystal X-ray and anti-*Candida* activity

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Abstract: The anti-*Candida* agent, (*E*)-3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one *O*-2-chlorobenzoyl oxime (**4**), has been synthesized and its crystal structure was presented. The compound crystallizes in the orthorhombic space group, $P2_12_12_1$ with a = 6.9088 (3) Å, b = 13.9001 (5) Å, c = 17.8749 (5) Å, α = 90.00 º, β = 90.00 º, γ = 90.00 º, V = 1716.58 (11) Å3, Z = 4. The crystal structure was stablized by weak intermolecular hydrogen C¯H···O. interactions.

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1. Introduction

The incidence and mortality of opportunistic fungal infection are rising dramatically in the last few decades. This is probably due to the relentless increase and spread of fungal resistance to the currently available antifungals together with the increased number of immune-compromised or immune-suppressed individuals which includes patients receiving cancer chemotherapy or organ transplantation and those with HIV infection (Caston-Osorio *et al*., 2008; Cuenca-Estrella *et al*., 2008). *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigates* are the most common species of human fungal pathogens giving rise to mortality rates of 20-40%, 20-70% and 50-90%, respectively (Lai *et al*., 2008; Park *et al*., 2009). Despite the introduction of several antifungal agents to the clinical chemotherapy, appropriate treatment of life-threatening fungal infections is still unmet and new additional antifungal drugs with improved efficacy are needed (Denning *et al*., 2006; Kathiravan *et al*., 2012). Clinically, azoles were widely used in the treatment of invasive fungal infections. Azoles act by competitive inhibition of lanosterol 14α-demethylase (CYP51), a key enzyme in sterol biosynthesis of fungi (Aoyama *et al*., 1984).

Examination of the literature has exposed that many of the available antifungal agents are fungistatic rather than fungicidal, while others are associated with a substantial toxicity and exhibit very complex structures (Kauffman and Carver, 2008; Maschmeyer and Haas, 2006). Accordingly, there is a continuing effort to develop novel and simpler antifungals which are more effective and less toxic.

It has been documented that some azole antifungals are derived from oxime-containing starting materials (Rossello *et al*., 2002). Herein, we report the synthesis, single crystal X-ray structure of the anti-*Candida* agent, (*E*)-3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one *O*-2-chlorobenzoyl oxime (**4**).

2. Experimental

2.1. General

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The X-ray diffraction measurements of compound **4** were performed using Bruker SMART APEXII CCD diffractometer. Crystallographic data of compound **4** has been deposited with the Cambridge Crystallographic Data Center (supplementary publication number **CCDC-969137**). Copies of the data may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

2.2. Preparation of 3-(1*H*-imidazol-1-yl)-1-phenyl-propan-1-one (2)

A mixture of acetophenone (2.4 g, 20 mmol), dimethylamine hydrochloride (2.2 g, 27 mmol) and paraformaldehyde (0.81 g, 9 mmol) was heated to reflux in absolute ethanol (5 mL) in the presence of a catalytic amount of concentrated hydrochloric acid (0.1 mL). The reaction mixture was refluxed for two hours, cooled and acetone (20 mL) was added. The precipitated Mannich base hydrochloride **1** (3.7 g, 17.4 mmol) was filtered, dried and subsequently dissolved in water (10 mL) and imidazole (2.4 g, 34.8 mmol) was added. The reaction mixture was heated

to reflux for five hours, cooled and the precipitated solid was filtered off to give the ketone **2** (2.7 g, 77%) mp 368-370 K (Aboul-Enein *et al*., 2011) which was pure enough to be used in the next step.

2.3. Preparation of (1*E*)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-imine (3)

The ketone **2** (2.00 g, 10 mmol), hydroxylamine hydrochloride (1.39 g, 20 mmol), and KOH (1.12 g, 20 mmol) in ethanol (10 mL) were heated to reflux under stirring for 18 hrs. The reaction mixture was cooled to room temperature and the insolubles were filtered off. The filtrate was concentrated under vacuum and the residue was poured onto ice-cold water (15 mL). The precipitated solid was filtered, dried, and recrystallized from ethanol to give 1.51 g (70%) of the oxime **3** as colorless crystals mp 428-430 K (Fun *et al.*, 2012).

2.4. Preparation of (*E*)-3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one *O*-2-chlorobenzoyl oxime (4)

A solution of the 2-chlorobenzoic acid (1.1 g, 7 mmol), EDCI.HCl (1.40 g, 7.3 mmol) and DMAP (400 mg) in DCM (75 mL) was stirred at ambient temperature. The oxime **3** (1.49 g, 6.9 mmol) was added to the stirred reaction mixture and stirring was continued for further 18 hrs at room temperature. The reaction mixture was washed successively with water (2 x 20 mL), 10% $NaHCO_3$ solution (2 x 15 mL), and water (2 x 15 mL). The organic layer was separated, dried (Na_2SO_4), evaporated under vacuum and the residue was recrystallized (isopropanol) to give 1.45 g (60%) of **4** as a white solid mp 391-393 K (Attia *et al*., 2013).

2.5. Crystal structure determination

Crystals of compound **4** were obtained by slow evaporation of pure **4** from isopropanol. A colorless single crystal of suitable size, 0.15 mm X 0.36 mm X 0.57 mm, was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD area diffractometer equipped with graphite monochromatic CuK\a radiation (λ = 1.54178 Å) at 296 K. Cell refinement and data reduction were done by Bruker SAINT (Brucker, 2009). The SHELTXL program was used to solve and refine the structure (Sheldrick, 2008). The final refinement was performed by full- matrix least-squares techniques with anisotropic thermal data for non hydrogen atoms on F^2. All the hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Multi-scan absorption correction was applied by use of SADABS software (Brucker, 2009). The crystallographic data and refinement information are summarized in Table 1.

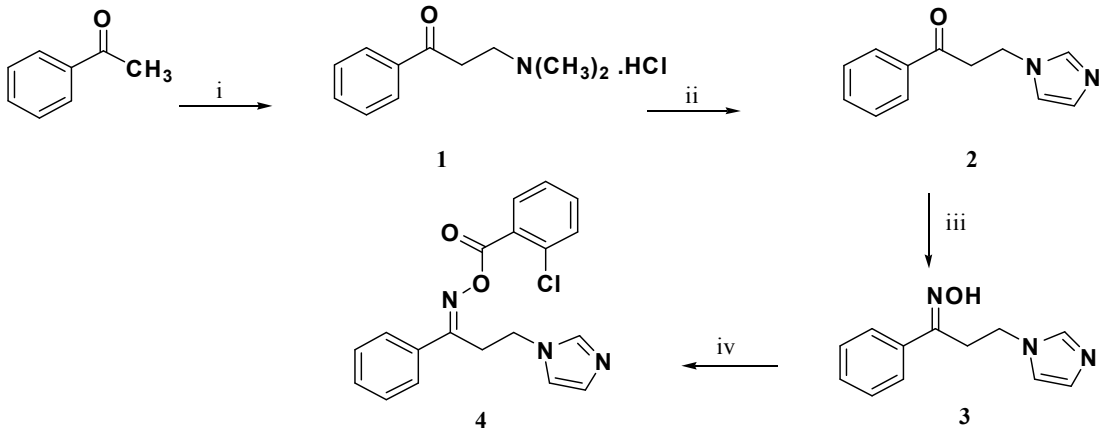
3. Results and Discussion

3.1. Chemistry

The synthetic pathway to produce the title compound **4** is depicited in Scheme 1. Acetophenone was transformed to the pivotal ketone **2** *via* Mannich reaction and subsequent alkylation of imidazole by Mannich base hydrochloride **1** to yield the ketone **2**. Compound **2** was reacted with hydroxylamine hydrochloride in the presence of potassium hydroxide to give the oxime **3**. Subsequent esterification of the hydroxyl group of compound **3** with 2-chlorobenzoic acid was successfully achieved in the presence of EDCI.HCl and DMAP to furnish the title compound **4**.

Table 1: The crystallographic data and refinement information.

Empirical formula	$C_{19}H_{16}ClN_3O_2$
Formula weight	353.80
Temperature (K)	296
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cu *K*α radiation, λ	1.54178 Å
a (Å)	6.9088 (3) (3)
b (Å)	13.9001 (5)
c (Å)	17.8749 (5)
α (º)	90.00
β (º)	90.00
γ (º)	90.00
V (Å^3)	1716.58 (11)
Z	4
F(000)	736
Theta range for data collection (º)	4.0 – 70.5
μ (mm^{-1})	2.12
Density (calc.) (g/cm^3)	1.369
Crystal shape and color	plate, colorless
Crystal size (mm^3)	0.57 × 0.36 × 0.15
h / *k* / *l*	−8,6/ −16,17/ −21,21
Measured reflections	12194
Independent reflections	3253 [R_{int} = 0.028]
Reflections with $I > 2\sigma(I)$	3096
Goodness-of-fit on F^2	1.04
$R[F^2 > 2\sigma(F^2)]$	0.035
$wR(F^2)$	0.092
$\Delta\rho_{max}$ (e Å^{-3})	0.17
$\Delta\rho_{min}$ (e Å^{-3})	−0.22



Scheme 1: Synthesis of the title compound **4**.

Reagents and conditions: i) $HN(CH_3)_2.HCl$, $(CH_2O)_n$, conc. HCl, ethanol, reflux, 2 hrs; ii) Imidazole, water, reflux, 5 hrs; iii) $H_2NOH.HCl$, KOH, ethanol, reflux, 18 hrs; iv) 2-Chlorobenzoic acid, EDCI.HCl, DMAP, DCM, rt, 18hrs.

3.2. Anti-*Candida* Activity

The *in vitro* anti-*Candida* activity of compound **4** was evaluated against two clinical isolates of *Candida*, namely *C. albicans* and *C. tropicalis*. The clinical isolates of *C. albicans* were considered practically resistant to the gold standard antifungal drug, Fluconazole (MIC >1.6325 µmol/mL). Compound **4** exhibited MIC values of 0.7069 and 0.3535 µmol/mL against *C. albicans* and *C. tropicalis*, respectively (Attia *et al*., 2013).

3.3. Crystal structure of compound 4

The crystal structure of the title compound **4** contains one molecule in the asymmetric unit. The labeled displacement ellipsoid plot of this molecule is shown in Figure 1. The selected bond lengths, bond angles and bond torsion angles are listed in Table 2. The weak interactions are listed in Table 3. Figure 2 depicts the packing of the molecules in the crystal structure. The crystal structure is stabilized by weak intermolecular C-H…O interactions into a three-dimensional framework.

Table 2: Selected geometric parameters (Å, °)

Cl1—C15	1.737 (2)	N1—C3	1.356 (2)
O1—N3	1.4403 (19)	N1—C4	1.458 (2)
O1—C13	1.346 (2)	N2—C1	1.303 (3)
O2—C13	1.186 (2)	N2—C2	1.361 (3)
N1—C1	1.348 (2)	N3—C6	1.280 (2)
N3—O1—C13	111.38 (13)	N1—C4—C5	113.04 (13)
C1—N1—C3	106.00 (15)	N3—C6—C5	124.53 (14)
C1—N1—C4	126.77 (15)	N3—C6—C7	114.71 (14)
C3—N1—C4	127.22 (15)	O1—C13—O2	124.35 (18)
C1—N2—C2	104.45 (18)	O1—C13—C14	112.17 (15)
O1—N3—C6	109.88 (13)	O2—C13—C14	123.34 (17)
N1—C1—N2	112.81 (17)	Cl1—C15—C14	121.96 (14)
N2—C2—C3	110.49 (19)	Cl1—C15—C16	116.59 (15)
N1—C3—C2	106.25 (18)		

Table 3: Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C11—H11A···O2^{i}	0.9300	2.5600	3.454 (2)	162.00

Symmetry code: (i) −*x*−1/2, −*y*+2, *z*−1/2.

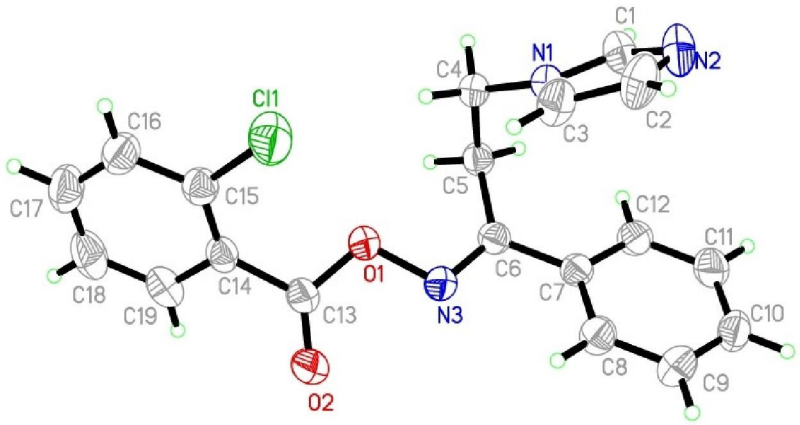


Figure 1: ORTEP diagram of compound **4** drawn at 50% ellipsoids for non-hydrogen atoms.

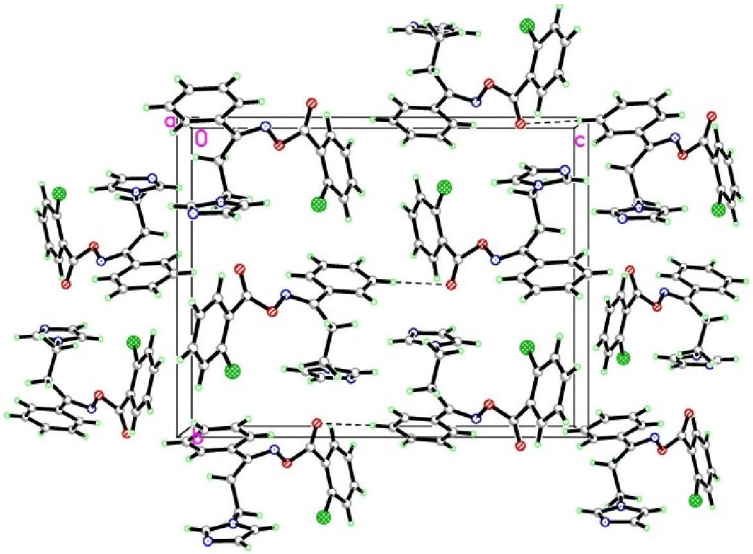


Figure 2: Crystal packing showing intermolecular C—H•••O hydrogen bonds as dashed lines.

4. Conclusion

The single crystal X-ray structure of the anti-*Candida* agent, namely (*E*)-3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one *O*-2-chlorobenzoyl oxime (**4**) is reported. The assigned (*E*)-configuration of the title compound **4** was confirmed *via* its single crystal X-ray structure.

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