Synthesis, structure elucidation, and antifungal potential of certain new benzodioxole–imidazole molecular hybrids bearing ester functionalities

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Background: The incidence of fungal infections is a growing serious global health burden. There is an urgent medical demand to acquire new antifungal drug-like compounds having azole nuclei to get rid of the drawbacks of the currently available azole antifungal agents.

Methods: The target compounds **5a–r** were synthesized in a four-step reaction sequence using the appropriate acetophenone derivative as a starting material. The antifungal potential of the title compounds was assessed using DIZ and MIC assays according to the reported standard procedures.

Results: The newly synthesized oximino esters **5a–r** were identified with the aid of various spectroscopic approaches. Their assigned chemical structures were confirmed via single-crystal X-ray structure of compound **5o**. The molecular structure of compound **5o** was crystallized in the triclinic, $P\bar{1}$, $a=9.898$ (3) Å, $b=10.433$ (3) Å, $c=11.677$ (4) Å, $\alpha=86.886$ (6)°, $\beta=87.071$ (7)°, $\gamma=64.385$ (6)°, $V=1,085.2$ (6) Å³, $Z=2$. The synthesized compounds **5a–r** were in vitro evaluated for antifungal potential against four fungal strains. Compounds **5l** and **5m** bearing a trifluoromethylphenyl moiety showed the best anti-*Candida albicans* activity with minimum inhibitory concentration (MIC) value of 0.148 µmol/mL, while compound **5b** displayed the best activity toward *Candida tropicalis* with MIC value of 0.289 µmol/mL. Compounds **5o** and **5l** were the most active congeners against *Candida parapsilosis* and *Aspergillus niger*, respectively.

Conclusion: Single-crystal X-ray analysis of compound **5o** confirmed without doubt the assigned chemical structures of the title compounds as well as confirmed the (*E*)-configuration of their oximino group. Compounds **5b**, **5l**, **5m**, and **5o** emerged as the most active compounds against the tested fungi and they could be considered as new antifungal lead candidates.

Keywords: crystal structure, imidazole, benzodioxole, ester, antifungal

Introduction

The incidence of fungal infections is a growing serious health burden worldwide, especially, in industrialized countries. Immunocompromised individuals are particularly more prone to life-threatening fungal infections caused by opportunistic fungi. In addition, the use of anticancer drugs and immunosuppressant agents increases the incidence rate of serious fungal infections. The emergence of drug resistance and toxicity of the currently available antifungal agents (flucytosine, amphotericin B, and ketoconazole) have reinforced the demand for the development of new antifungal candidates with improved potency and safety profiles.^{1,2}

Azoles are successfully used for the treatment of serious fungal infections owing to their favorable pharmacokinetic parameters, high therapeutic index, and wide antifungal spectrum.³ They inhibit the activity of lanosterol 14 α -demethylase (CYP51) leading to prevention of ergosterol biosynthesis and hence the inability of fungi to grow normally.⁴

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Imidazole and triazole heterocyclic rings constitute essential pharmacophore fragments of the clinically used antifungal azoles. Fluconazole and itraconazole are potent triazole-bearing antifungal drugs; however, the former drug is not effective against invasive aspergillosis and the latter one suffers from poor aqueous solubility and oral bioavailability.^{5,6} Therefore, there is an urgent medical need to develop new antifungal drug-like candidates bearing azole nuclei to overcome the drawbacks of the currently available azole antifungal agents.

Most of the available azole antifungal agents bear an ethyl spacer which separates the azole moiety from an aromatic pharmacophore fragment. However, a propyl spacer separating the azole pharmacophore from the aromatic part occurred in a limited number of antifungal candidates.^{7–9} Accordingly, it was of our interest to report the synthesis of certain imidazole-based surrogates bearing a propyl spacer to be evaluated as new antifungal candidates. In addition, the title compounds **5a–r** bear 1,3-benzodioxole aromatic fragments which might augment their antifungal potential.^{10,11} The assigned chemical structures of the target compounds **5a–r** were thoroughly characterized using different spectroscopic techniques. Moreover, the configuration of the imine functionality of the title compounds **5a–r** were examined with the aid of single crystal X-ray analysis of compound **5o** as a representative example of the title compounds **5a–r**.

Materials and methods

General

The uncorrected melting points of the synthesized compounds were measured using a Gallenkamp melting point device. A Perkin Elmer FT-IR Spectrum BX device was used to record the infrared (IR) spectra (as KBr disks). The nuclear magnetic resonance (NMR) spectra of the synthesized compounds were measured after dissolving the test samples in DMSO-*d*₆ and the measurements were achieved at 500 MHz for ¹H and 125.76 MHz for ¹³C on Bruker NMR spectrometer at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are articulated in δ -values (ppm) compared to tetramethylsilane as an internal standard. Elemental analyses of the target compounds were executed at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, and the results agreed favorably with the proposed structure within $\pm 0.4\%$ of the theoretical values (Table S1). Agilent Quadrupole 6120 LC/MS was utilized to record the mass spectra of the synthesized compounds with the aid of electrospray ionization (ESI) source. Silica gel thin layer chromatography plates with fluorescent indicator at 254 nm were acquired from Merck and visualization was accomplished by illumination with a UV light source (254 nm).

Chemistry

Synthesis of 1-(2*H*-1,3-benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propan-1-one (**3**)

Compound **3** was prepared according to the previously reported procedure and its spectral data are consistent with reported ones.¹²

Synthesis of (1*E*)-1-(2*H*-1,3-benzodioxol-5-yl)-*N*-hydroxy-3-(1*H*-imidazol-1-yl)propan-1-imine (**4**)

Oxime **4** was synthesized from ketone **3** through adopting the reported method and its spectral data are consistent with the previously reported ones.¹³

General procedure for the synthesis of the target oximino esters **5a–r**

Method A

N,N'-Carbonyldiimidazole (0.32 g, 2.0 mmol) was added to a stirred solution of the appropriate carboxylic acid (2.0 mmol) in tetrahydrofuran (THF) (10 mL). Oxime **4** (0.5 g, 2.0 mmol) was added to the stirred reaction mixture and stirring was continued for further 18 hours at room temperature. THF was evaporated under vacuum and ethyl acetate (30 mL) was added to the residue and the organic phase was washed successively with water (2×20 mL), 10% NaHCO₃ solution (2×15 mL), and water (2×15 mL). The organic layer was separated, dried (Na₂SO₄), and evaporated under reduced pressure. The corresponding oximino esters **5a–d**, **5f**, **5g**, **5i**, **5l**, **5m**, and **5p–r** were purified either by recrystallization from ethanol (for solids) or column chromatography (for oils).

Method B

4-Dimethylaminopyridine (400 mg) was added to a stirred solution of the appropriate carboxylic acid (7 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI·HCl, 1.39 g, 7.3 mmol) in dichloromethane (75 mL). Oxime **4** (1.79 g, 6.9 mmol) was added to the stirred reaction mixture and stirring was continued for further 18 hours at room temperature. The reaction mixture was washed successively with water (2×20 mL), 10% NaHCO₃ solution (2×15 mL), and water (2×15 mL). The organic layer was separated, dried (Na₂SO₄), and evaporated under reduced pressure. The respective crude oximino esters **5e**, **5h**, **5j**, **5k**, **5n**, and **5o** were purified by recrystallization from ethanol.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(phenyl)methanone (**5a**). Yield 0.28 g (28%); white powder, mp 130°C–132°C; IR (KBr): ν (cm⁻¹) 3,099, 2,887, 1,739 (C=O), 1,600 (C=N), 1,504, 1,452, 1,232, 744; ¹H-NMR (CDCl₃): δ (ppm) 3.44 (t, *J* = 7.0 Hz, 2H, -CH₂-CH₂-N), 4.36 (t, *J* = 7.0 Hz,

2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.05 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.84 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.95 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.07 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.14 (d, $J = 7.0$ Hz, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.52–7.55 (m, 2H, Ar-H), 7.64–7.66 (m, 1H, Ar-H), 7.83 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 8.05 (d, $J = 7.5$ Hz, 2H, Ar-H); ^{13}C -NMR (CDCl_3): δ (ppm) 30.7 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 44.2 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.8 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.5 (Ar-CH), 119.1 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.1, 126.8, 128.7, 128.8, 129.5, 133.7 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 136.8 ($-\text{N}-\text{CH}=\text{N}-$), 148.5, 150.5 (Ar-C), 162.6, 163.4 (C=N, C=O); MS m/z (ESI): 364.1 $[\text{M} + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}$ (4-bromophenyl)methanone (**5b**). Yield 0.34 g (34%); pale yellow powder, mp 92°C – 94°C ; IR (KBr): ν (cm^{-1}) 3,107, 2,914, 1,726 (C=O), 1,589 (C=N), 1,504, 1,442, 1,265, 748; ^1H -NMR (CDCl_3): δ (ppm) 3.43 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.34 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.06 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.85 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.93 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.05 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.14 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.31 (d, $J = 1.0$ Hz, 1H, Ar-H), 7.67 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.82 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.87 (d, $J = 8.5$ Hz, 2H, Ar-H); ^{13}C -NMR (CDCl_3): δ (ppm) 30.6 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 44.2 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.9 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.5 (Ar-CH), 119.1 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.1, 126.5, 127.5, 128.7, 128.9, 131.0, 132.2 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 136.8 ($-\text{N}-\text{CH}=\text{N}-$), 148.6, 150.6 (Ar-C), 162.8, 162.9 (C=N, C=O); MS m/z (ESI): 442.0 $[\text{M} + \text{H}]^+$, 444.0 $[(\text{M} + 2) + \text{H}]^+$, 445.0 $[(\text{M} + 3) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}$ (2-chlorophenyl)methanone (**5c**). Yield 0.53 g (53%); pale yellow viscous oil; IR (KBr): ν (cm^{-1}) 3,016, 2,937, 1,739 (C=O), 1,604 (C=N), 1,510, 1,446, 1,253, 754; ^1H -NMR (CDCl_3): δ (ppm) 3.35 (t, $J = 6.6$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.23 (t, $J = 6.6$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.07 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.81 (d, $J = 7.8$ Hz, 1H, Ar-H), 6.86 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 6.98 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.09 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 7.42 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.48–7.50 (m, 2H, Ar-H), 7.79 (d, $J = 7.2$ Hz, 1H, Ar-H); ^{13}C -NMR (CDCl_3): δ (ppm) 31.0 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.9 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.8 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.5 (Ar-CH), 118.7 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.1, 126.5, 127.0, 129.4, 129.8, 130.9, 131.7, 132.9, 133.1 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 136.8 ($-\text{N}-\text{CH}=\text{N}-$), 148.5, 150.5 (Ar-C), 162.8, 163.3 (C=N, C=O); MS m/z (ESI): 398.1 $[\text{M} + \text{H}]^+$, 399.1 $[(\text{M} + 1) + \text{H}]^+$, 400.1 $[(\text{M} + 2) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}$ (3-chlorophenyl)methanone (**5d**). Yield 0.39 g (39%); white powder, mp 118°C – 121°C ; IR (KBr): ν (cm^{-1}) 3,064, 2,922, 1,735 (C=O), 16,24 (C=N),

1,575, 1,504, 1,232, 736; ^1H -NMR (CDCl_3): δ (ppm) = 3.40 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.30 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.06 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.85 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.94 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.05 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.13 (dd, $J = 1.5, 8.0$ Hz, 1H, Ar-H), 7.29–7.30 (m, 1H, Ar-H), 7.46–7.49 (m, 2H, $-\text{N}-\text{CH}=\text{N}-$, Ar-H), 7.63 (dd, $J = 0.9, 7.9$ Hz, 1H, Ar-H), 7.91 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.01 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3): δ (ppm) 30.7 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.9 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.9 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.5 (Ar-CH), 118.8 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.1, 126.5, 127.7, 129.6, 130.0, 130.1, 130.4, 133.7, 134.9 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 136.9 ($-\text{N}-\text{CH}=\text{N}-$), 148.6, 150.6 (Ar-C), 162.3, 163.1 (C=N, C=O); MS m/z (ESI): 398.1 $[\text{M} + \text{H}]^+$, 399.1 $[(\text{M} + 1) + \text{H}]^+$, 400.1 $[(\text{M} + 2) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}$ (4-chlorophenyl)methanone (**5e**). Yield 0.37 g (37%); white powder, mp 103°C – 105°C ; IR (KBr): ν (cm^{-1}) 3,111, 2,912, 1,730 (C=O), 1,589 (C=N), 1,504, 1,444, 1,255, 750; ^1H -NMR (CDCl_3): δ (ppm) 3.43 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.34 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.05 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.84 (d, $J = 8.5$ Hz, 1H, Ar-H), 6.93 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.05 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.14 (dd, $J = 1.5, 8.5$ Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.48 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.83 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.94 (d, $J = 8.5$ Hz, 2H, Ar-H); ^{13}C -NMR (CDCl_3): δ (ppm) 30.6 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 44.2 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.9 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.5 (Ar-CH), 119.1 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.1, 126.5, 127.0, 128.6, 129.2, 130.9 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 136.8 ($-\text{N}-\text{CH}=\text{N}-$), 140.2, 148.5, 150.6 (Ar-C), 162.6, 162.8 (C=N, C=O); MS m/z (ESI): 398.1 $[\text{M} + \text{H}]^+$, 399.1 $[(\text{M} + 1) + \text{H}]^+$, 400.1 $[(\text{M} + 2) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}$ (3-fluorophenyl)methanone (**5f**). Yield 0.4 g (40%); white powder, mp 135°C – 137°C ; IR (KBr): ν (cm^{-1}) 3,007, 1,741 (C=O), 1,703 (C=N), 1,589, 1,506, 1,267, 746; ^1H -NMR ($\text{DMSO}-d_6$): δ (ppm) 3.47 (t, $J = 6.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.27 (t, $J = 6.1$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.14 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.78 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.04 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.16 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.32 (s, 2H, Ar-H), 7.55 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.60–7.67 (m, 2H, Ar-H), 7.77 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.88 (d, $J = 7.4$ Hz, 1H, Ar-H); ^{13}C -NMR ($\text{DMSO}-d_6$): δ (ppm) 30.4 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.7 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.3 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 116.4, 119.8, 121.2, 121.3, 122.9, 126.1, 126.2, 127.1, 128.9 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 137.6 ($-\text{N}-\text{CH}=\text{N}-$), 148.3, 150.3, 162.3, 163.5, 164.7 (Ar-C, C=N, C=O); MS m/z (ESI): 382.1 $[\text{M} + \text{H}]^+$, 383.1 $[(\text{M} + 1) + \text{H}]^+$.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(4-fluorophenyl)methanone (**5g**). Yield 0.35 g (35%); white powder, mp 75°C–77°C; IR (KBr): ν (cm⁻¹) 3,107, 2,920, 1,739 (C=O), 1,602 (C=N), 1,583, 1,506, 1,246, 756; ¹H-NMR (CDCl₃): δ (ppm) 3.40 (t, *J* = 6.9 Hz, 2H, –CH₂–CH₂–N), 4.30 (t, *J* = 6.9 Hz, 2H, –CH₂–CH₂–N), 6.05 (s, 2H, –O–CH₂–O–), 6.85 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.92 (s, 1H, –N–CH=CH–N=), 7.04 (s, 1H, –N–CH=CH–N=), 7.14 (dd, *J* = 1.5, 8.1 Hz, 1H, Ar-H), 7.18–7.22 (m, 2H, Ar-H), 7.28–7.29 (m, 1H, Ar-H), 7.57 (s, 1H, –N–CH=N–), 8.03–8.06 (m, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ (ppm) 30.7 (–CH₂–CH₂–N), 43.9 (–CH₂–CH₂–N), 101.9 (–O–CH₂–O–), 107.2, 108.5 (Ar-CH), 116.1 (d, *J* C-3', F & C-5', *F* = 22.1 Hz, C-3' and C-5'), 118.9 (–N–CH=CH–N=), 122.1, 124.9, 126.7, 129.7 (Ar-CH, Ar-C, –N–CH=CH–N=), 132.2 (d, *J* C-2', F & C-6', *F* = 9.4 Hz, C-2' and C-6'), 136.9 (–N–CH=N–), 148.5, 150.5, 162.6, 162.8, (Ar-C, C=N, C=O), 166.1 (d, *J* C-4', *F* = 255.8 Hz, C-4'); MS *m/z* (ESI): 382.1 [M + H]⁺, 383.1 [(M + 1) + H]⁺.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(4-methoxyphenyl)methanone (**5h**). Yield 0.63 g (63%); white powder, mp 147°C–149°C; IR (KBr): ν (cm⁻¹) 3,015, 2,966, 1,722 (C=O), 1,604 (C=N), 1,506, 1,440, 1,259, 740; ¹H-NMR (CDCl₃): δ (ppm) 3.41 (t, *J* = 6.5 Hz, 2H, –CH₂–CH₂–N), 3.90 (s, 3H, –OCH₃), 4.34 (t, *J* = 6.5 Hz, 2H, –CH₂–CH₂–N), 6.03 (s, 2H, –O–CH₂–O–), 6.82 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.95 (s, 1H, –N–CH=CH–N=), 6.98 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.05 (s, 1H, –N–CH=CH–N=), 7.12 (dd, *J* = 1.5, 8.0 Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.79 (s, 1H, –N–CH=N–), 7.97 (d, *J* = 9.0 Hz, 2H, Ar-H.); ¹³C-NMR (CDCl₃): δ (ppm) 30.7 (–CH₂–CH₂–N), 44.2 (–CH₂–CH₂–N), 55.6 (–OCH₃), 101.8 (–O–CH₂–O–), 107.1, 108.4, 114.1 (Ar-CH), 119.1 (–N–CH=CH–N=), 120.7, 122.0, 126.9, 128.7, 131.6 (Ar-CH, Ar-C, –N–CH=CH–N=), 136.8 (–N–CH=N–), 148.6, 150.4, 162.2 (Ar-C), 163.2, 163.9 (C=N, C=O); MS *m/z* (ESI): 394.1 [M + H]⁺, 416.1 [M + 23]⁺.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(2-methylphenyl)methanone (**5i**). Yield 0.4 g (40%); pale yellow viscous oil; IR (KBr): ν (cm⁻¹) 3,014, 2,966, 1,747 (C=O), 1,600 (C=N), 1,506, 1,444, 12,32, 710; ¹H-NMR (CDCl₃): δ (ppm) 2.64 (s, 3H, CH₃), 3.35 (t, *J* = 6.6 Hz, 2H, –CH₂–CH₂–N), 4.24 (t, *J* = 6.6 Hz, 2H, –CH₂–CH₂–N), 6.02 (s, 2H, –O–CH₂–O–), 6.82 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.87 (s, 1H, –N–CH=CH–N=), 7.05 (s, 1H, –N–CH=CH–N=), 7.11 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.22–7.26 (m, 1H, Ar-H.), 7.30–7.32 (m, 2H, Ar-H.), 7.46 (t, *J* = 7.2 Hz, 1H, Ar-H.), 7.56 (s, 1H, –N–CH=N–), 7.77 (d, *J* = 7.8 Hz, 1H, Ar-H); ¹³C-NMR (CDCl₃): δ (ppm) 21.8 (CH₃), 30.7 (–CH₂–CH₂–N), 44.0

(–CH₂–CH₂–N), 101.8 (–O–CH₂–O–), 107.1, 108.4 (Ar-CH), 118.8 (–N–CH=CH–N=), 122.0, 125.9, 126.8, 128.0, 129.2, 129.7, 130.8, 132.0 (Ar-CH, Ar-C, –N–CH=CH–N=), 136.8 (–N–CH=N–), 140.8, 148.5, 150.4 (Ar-C), 162.1, 164.2 (C=N, C=O); MS *m/z* (ESI): 378.1 [M + H]⁺.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(3-methylphenyl)methanone (**5j**). Yield 0.36 g (36%); white powder, mp 103°C–105°C; IR (KBr): ν (cm⁻¹) 3,107, 2,978, 1,743 (C=O), 1,610 (C=N), 1,575, 1,502, 1,269, 720; ¹H-NMR (CDCl₃): δ (ppm) 2.45 (s, 3H, CH₃), 3.42 (t, *J* = 7.0 Hz, 2H, –CH₂–CH₂–N), 4.34 (t, *J* = 7.0 Hz, 2H, –CH₂–CH₂–N), 6.03 (s, 2H, –O–CH₂–O–), 6.83 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.96 (s, 1H, –N–CH=CH–N=), 7.05 (s, 1H, –N–CH=CH–N=), 7.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.30 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.40–7.44 (m, 2H, Ar-H.), 7.74 (s, 1H, –N–CH=N–), 7.81 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃): δ (ppm) 21.4 (CH₃), 30.7 (–CH₂–CH₂–N), 44.2 (–CH₂–CH₂–N), 101.8 (–O–CH₂–O–), 107.2, 108.5 (Ar-CH), 119.1 (–N–CH=CH–N=), 122.1, 126.6, 126.8, 128.6, 128.7, 128.8, 130.1, 134.5 (Ar-CH, Ar-C, –N–CH=CH–N=), 136.8 (–N–CH=N–), 138.7, 148.5, 150.5 (Ar-C), 162.6, 163.6 (C=N, C=O); MS *m/z* (ESI): 378.1 [M + H]⁺.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)(4-methylphenyl)methanone (**5k**). Yield 0.3 g (30%); pale yellow powder, mp 73°C–76°C; IR (KBr): ν (cm⁻¹) 3,107, 2,920, 1,722 (C=O), 1,612 (C=N), 1,581, 1,504, 1,265, 742; ¹H-NMR (CDCl₃): δ (ppm) 2.41 (s, 3H, CH₃), 3.41 (t, *J* = 6.5 Hz, 2H, –CH₂–CH₂–N), 4.33 (t, *J* = 7.0 Hz, 2H, –CH₂–CH₂–N), 6.04 (s, 2H, –O–CH₂–O–), 6.84 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.95 (s, 1H, –N–CH=CH–N=), 7.05 (s, 1H, –N–CH=CH–N=), 7.13 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.32 (d, *J* = 8.0 Hz, 2H, Ar-H.), 7.67 (s, 1H, –N–CH=N–), 7.93 (d, *J* = 8.0 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃): δ (ppm) 21.8 (CH₃), 30.8 (–CH₂–CH₂–N), 44.1 (–CH₂–CH₂–N), 101.7 (–O–CH₂–O–), 107.2, 108.5 (Ar-CH), 118.9 (–N–CH=CH–N=), 122.0, 125.8 (Ar-CH), 126.9, 129.2, 129.5, 129.6 (Ar-C, –N–CH=CH–N=), 136.9 (–N–CH=N–), 144.6, 148.5, 150.4 (Ar-C), 162.4, 163.5 (C=N, C=O); MS *m/z* (ESI): 378.1 [M + H]⁺.

({[(1*E*)-1-(1,3-Benzodioxol-5-yl)-3-(1*H*-imidazol-1-yl)propylidene]amino}oxy)[(3-(trifluoromethyl)phenyl)]methanone (**5l**). Yield 0.38 g (38%); white powder, mp 129°C–131°C; IR (KBr): ν (cm⁻¹) 3,089, 1,753 (C=O), 1,612 (C=N), 1,579, 1,500, 1,228, 744; ¹H-NMR (DMSO-*d*₆): δ (ppm) 3.48 (t, *J* = 6.4 Hz, 2H, –CH₂–CH₂–N), 4.29 (t, *J* = 6.4 Hz, 2H, –CH₂–CH₂–N), 6.14 (s, 2H, –O–CH₂–O–), 6.77 (s, 1H, –N–CH=CH–N=), 7.04 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.16 (s, 1H, –N–CH=CH–N=), 7.34–7.36 (m, 2H, Ar-H), 7.54 (s, 1H, –N–CH=N–), 7.84–7.87 (m, 1H, Ar-H),

8.11 (d, $J = 7.5$ Hz, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 8.31 (d, $J = 7.6$ Hz, 1H, Ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 30.5 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.8 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.3 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 119.8 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 122.9, 126.1, 126.2, 127.0, 128.9, 130.0, 130.7, 130.8, 130.9, 133.8 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 137.6, 148.4, 150.4 ($-\text{N}-\text{CH}=\text{N}-$, Ar-C), 162.2, 164.8 (C=N, C=O); MS m/z (ESI): 432.1 $[\text{M} + \text{H}]^+$, 433.1 $[(\text{M} + 1) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}[(4\text{-}(trifluoromethyl)\text{phenyl})]\text{methanone}$ (**5m**). Yield 0.35 g (35%); white powder, mp 136°C – 138°C ; IR (KBr): ν (cm^{-1}) 3,026, 2,939, 1,741 (C=O), 1,624 (C=N), 1,577, 1,510, 1,251, 742; $^1\text{H-NMR}$ (DMSO- d_6): δ (ppm) 3.48 (t, $J = 6.3$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.28 (t, $J = 6.4$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.14 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.79 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.04 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.16 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.32–7.34 (m, 2H, Ar-H), 7.56 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.96 (d, $J = 8.0$ Hz, 2H, Ar-H), 8.22 (d, $J = 7.9$ Hz, 2H, Ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6): δ (ppm) 30.4 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.6 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.3 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 119.9 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 122.9, 126.3, 126.4, 127.0, 128.9, 130.8, 132.7, 133.5 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 137.7 ($-\text{N}-\text{CH}=\text{N}-$), 148.4, 150.3 (Ar-C), 162.3, 164.8 (C=N, C=O); MS m/z (ESI): 432.1 $[\text{M} + \text{H}]^+$, 433.1 $[(\text{M} + 1) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}(3,4\text{-dichlorophenyl})\text{methanone}$ (**5n**). Yield 0.48 g (48%); white powder, mp 180°C – 183°C ; IR (KBr): ν (cm^{-1}) 3,088, 2,958, 1,737 (C=O), 1,573 (C=N), 1,506, 1,469, 1,230, 748; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 3.38 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.29 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.07 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.86 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.93 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.05 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.15 (dd, $J = 1.0, 8.0$ Hz, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.53 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.60 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.82 (dd, $J = 1.5, 8.0$ Hz, 1H, Ar-H), 8.08 (d, $J = 1.5$ Hz, 1H, Ar-H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 30.7 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.9 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 101.9 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.2, 108.6 (Ar-CH), 118.8 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 122.2, 126.3, 128.5, 128.6, 130.0, 131.0, 131.4, 133.4 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 136.9 ($-\text{N}-\text{CH}=\text{N}-$), 138.4, 148.6, 150.7 (Ar-C), 161.7, 163.2 (C=N, C=O); MS m/z (ESI): 432.0 $[\text{M} + \text{H}]^+$, 433.0 $[(\text{M} + 1) + \text{H}]^+$, 434.0 $[(\text{M} + 2) + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}(3,4,5\text{-trimethoxyphenyl})\text{methanone}$ (**5o**). Yield 0.65 g (65%); white powder, mp 178°C – 180°C ; IR (KBr): ν (cm^{-1}) 3,109, 2,941, 1,739 (C=O), 1,583 (C=N), 1,502, 1,462, 1,240, 736; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 3.40 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 3.94 (s,

6H, 2 x $-\text{OCH}_3$), 3.95 (s, 3H, $-\text{OCH}_3$), 4.30 (t, $J = 7.0$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.05 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.85 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.93 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.04 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.12 (dd, $J = 1.5, 8.0$ Hz, 1H, Ar-H), 7.28–7.29 (m, 3H, Ar-H), 7.51 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 30.8 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.9 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 56.4, 61.0 ($-\text{OCH}_3$), 101.9 ($-\text{O}-\text{CH}_2-\text{O}-$), 106.9, 107.2, 108.5 (Ar-CH), 118.7 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 122.1, 123.5, 126.7, 130.0 (Ar-CH, Ar-C, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 136.8 ($-\text{N}-\text{CH}=\text{N}-$), 143.0, 148.5, 150.5, 153.2 (Ar-C), 162.8, 163.2 (C=N, C=O); MS m/z (ESI): 454.2 $[\text{M} + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}(\text{pyridine-4-yl})\text{methanone}$ (**5p**). Yield 0.44 g (44%); white powder, mp 175°C – 177°C ; IR (KBr): ν (cm^{-1}) 3,145, 2,914, 1,747 (C=O), 1,589 (C=N), 1,504, 1,442, 1,230, 729; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 3.48 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.28 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.14 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.77 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.03 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.16 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.32 (s, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.55 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.91 (dd, $J = 1.5, 4.5$ Hz, 2H, pyridine-H), 8.86 (dd, $J = 1.5, 4.5$ Hz, 2H, pyridine-H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 30.4 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.6 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.3 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 119.9 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 123.0, 123.1, 126.9 (Ar-CH), 128.9 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 136.2 ($-\text{N}-\text{CH}=\text{N}-$), 137.7, 148.3, 150.4, 151.3 (Ar-C), 162.2, 165.1 (C=N, C=O); MS m/z (ESI): 365.1 $[\text{M} + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}(\text{thiophen-2-yl})\text{methanone}$ (**5q**). Yield 0.28 g (28%); white powder, mp 149°C – 151°C ; IR (KBr): ν (cm^{-1}) 3,099, 2,889, 1,734 (C=O), 1,577 (C=N), 1,504, 1,452, 1,246, 729; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 3.42 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.27 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.13 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.82 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.02 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.18 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 7.29–7.33 (m, 3H, Ar-H, thiophene-H), 7.58 (s, 1H, $-\text{N}-\text{CH}=\text{N}-$), 7.97 (dd, $J = 1.0, 3.5$ Hz, 1H, thiophene-H), 8.08 (dd, $J = 1.0, 4.5$ Hz, 1H, thiophene-H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) 30.5 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.5 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.3 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 119.8 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 122.9, 127.1, 128.9, 129.1 (Ar-CH), 131.3 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{N}$), 135.1, 135.3, (Ar-C) 137.6, ($-\text{N}-\text{CH}=\text{N}-$) 148.3, 150.2 (Ar-C), 159.0, 163.9 (C=N, C=O); MS m/z (ESI): 370.1 $[\text{M} + \text{H}]^+$.

($\{[(1E)-1-(1,3\text{-Benzodioxol-5-yl})-3-(1H\text{-imidazol-1-yl})\text{propylidene}]\text{amino}\}\text{oxy}\}(\text{thiophen-3-yl})\text{methanone}$ (**5r**). Yield 0.43 g (43%); white powder, mp 138°C – 140°C ; IR (KBr): ν (cm^{-1}) 3,144, 2,887, 1,739 (C=O), 1,577 (C=N), 1,504, 1,450, 1,230, 727; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) 3.44

(t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 4.26 (t, $J = 6.5$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{N}$), 6.13 (s, 2H, $-\text{O}-\text{CH}_2-\text{O}-$), 6.79 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.01 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.16 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.28–7.29 (m, 2H, Ar-H), 7.56 (s, 1H, $-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 7.57 (d, $J = 5.5$ Hz, 1H, thiophene-H), 7.75 (dd, $J = 3.0, 5.0$ Hz, 1H, thiophene-H), 8.53 (d, $J = 1.5$ Hz, 1H, thiophene-H); ^{13}C -NMR (CDCl_3): δ (ppm) 30.3 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 43.6 ($-\text{CH}_2-\text{CH}_2-\text{N}$), 102.2 ($-\text{O}-\text{CH}_2-\text{O}-$), 107.4, 108.9 (Ar-CH), 119.9 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 122.8, 127.3, 127.9, 128.4 (Ar-CH), 128.9 ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 131.4, 135.1, (Ar-C) 137.7, ($-\text{N}-\text{CH}=\text{CH}-\text{N}=\text{)$, 148.3, 150.1 (Ar-C), 159.5, 163.9 (C=N, C=O); MS m/z (ESI): 370.1 $[\text{M} + \text{H}]^+$.

Crystal structure determination of compound 5o

Compound **5o** was obtained as single crystals by slow evaporation from ethanol solution of the pure compound at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å at 293 (2) K. Cell refinement and data reduction were carried out by Bruker

SAINT. SHELXT¹⁴ was used to solve the structure. The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on F. CCDC 1875757 contains the supplementary crystallographic data for this compound and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Antifungal activity of the title compounds 5a-r

The in vitro antifungal potential of the oximino esters **5a-r** was examined with the aid of diameter of the inhibition zone (DIZ) and minimum inhibitory concentration (MIC) assays according to literature methods.¹² The detailed experimental procedures are provided under the “Antifungal activity” section of in the Supplementary materials.

Results and discussion

Chemistry

The adopted synthetic pathway to prepare the title compounds **5a-r** is portrayed in Scheme 1. Thus, the reaction sequence

Compound no	R	Compound no	R	Compound no	R
5a	C_6H_5	5g	4 F- C_6H_4	5m	4- CF_3 - C_6H_4
5b	4-Br- C_6H_4	5h	4- OCH_3 - C_6H_4	5n	3,4 Cl_2 - C_6H_3
5c	2 Cl- C_6H_4	5i	2- CH_3 - C_6H_4	5o	3,4,5-(OCH_3) ₃ - C_6H_2
5d	3 Cl- C_6H_4	5j	3- CH_3 - C_6H_4	5p	4- $\text{C}_8\text{H}_4\text{N}$
5e	4 Cl- C_6H_4	5k	4- CH_3 - C_6H_4	5q	2- $\text{C}_4\text{H}_3\text{S}$
5f	3 F- C_6H_4	5l	3- CF_3 - C_6H_4	5r	3- $\text{C}_4\text{H}_3\text{S}$

Scheme 1 Synthesis of the target compounds **5a-r**. Reagents and conditions: (i) $\text{HN}(\text{CH}_3)_2\cdot\text{HCl}$, $(\text{CH}_2\text{O})_n$, concentrated HCl, ethanol, reflux, 2 hours; (ii) imidazole, water, reflux, 5 hours; (iii) $\text{H}_2\text{NOH}\cdot\text{HCl}$, KOH, ethanol, reflux, 18 hours; (iv) N,N' -carbonyldiimidazole, ArCOOH , THF, rt, 18 hours, for compounds **5a-d**, **5f**, **5g**, **5i**, **5l**, **5m**, and **5p-r**; and (v) ArCOOH , EDCI.HCl, DMAP, DCM, rt, 18 hours, for compounds **5e**, **5h**, **5j**, **5k**, **5n**, and **5o**.

Abbreviations: DCM, dichloromethane; DMAP, 4-dimethylaminopyridine; rt, room temperature; THF, tetrahydrofuran.

was commenced via conducting a Mannich reaction on the commercially available 1,3-benzodioxole derivative **1** to achieve oxime **3** in a three-step reaction sequence according to the reported methods.¹³ Compound **3** was subjected to esterification with the appropriate carboxylic acid under mild conditions to furnish the target oximino esters **5a-r** in acceptable yields.

Crystal structure of compound **5o**

The crystallographic data and refinement information of compound **5o**, C₂₃H₂₄N₄O₆, are summarized in Table 1. The selected bond lengths and bond angles for compound **5o** are presented in Table 2. The asymmetric unit contains one independent molecule as shown in Figure 1. The 1,3-benzodioxole plane makes dihedral angles 5.69° and 77.56° with trimethoxyphenyl ring and imidazole ring, respectively. All the bond lengths and angles are in normal ranges.¹⁵ The molecules are packed together in the crystal structure by three non-classical hydrogen bonds along the *b* axis as shown in Table 3 and Figure 2.

Table 1 The crystallographic data and refinement information of compound **5o**

Crystal data	
Molecular formula	C ₂₃ H ₂₄ N ₄ O ₆
Molecular weight	452.46
Crystal system, space group	Triclinic, <i>P</i> -1
Temperature (K)	293
<i>a</i> , <i>b</i> , <i>c</i> (Å)	9.898 (3), 10.433 (3), 11.677 (4)
α , β , γ (°)	86.886 (6), 87.071 (7), 64.385 (6)
<i>V</i> (Å ³)	1,085.2 (6)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.10
Crystal size (mm)	0.15×0.08×0.08
Data collection	
Diffractometer	Bruker APEX-II D8 venture diffractometer
Absorption correction	Multi-scan SADABS Bruker 2014
<i>T</i> _{min} , <i>T</i> _{max}	0.862, 0.903
No of measured, independent, and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	24,341, 3,808, 1,363
<i>R</i> _{int}	0.408
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.100, 0.263, 1.02
No of reflections	3,808
No of parameters	301
No of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å ⁻³)	0.42, -0.56

Table 2 Selected geometric parameters (Å, °) of compound **5o**

O1–C1	1.374 (10)	O6–C23	1.428 (8)
O1–C7	1.434 (9)	N1–C10	1.461 (9)
O2–C6	1.374 (9)	N1–C11	1.358 (11)
O2–C7	1.417 (9)	N1–C13	1.329 (10)
O3–C14	1.220 (9)	N2–C12	1.344 (12)
O4–C17	1.354 (8)	N2–C13	1.314 (13)
O4–C21	1.427 (10)	N3–N4	1.423 (8)
O5–C18	1.360 (10)	N3–C8	1.296 (9)
O5–C22	1.358 (11)	N4–C14	1.341 (8)
O6–C19	1.359 (9)		
C1–O1–C7	106.0 (5)	N3–C8–C4	112.5 (6)
C6–O2–C7	105.5 (5)	N3–C8–C9	124.1 (6)
C17–O4–C21	118.6 (6)	N1–C10–C9	112.5 (6)
C18–O5–C22	123.8 (6)	N1–C11–C12	106.1 (7)
C19–O6–C23	118.0 (5)	N2–C12–C11	111.3 (8)
C10–N1–C11	129.0 (6)	N1–C13–N2	113.9 (8)
C10–N1–C13	125.7 (7)	O3–C14–C15	124.4 (6)
C11–N1–C13	105.3 (7)	O3–C14–N4	122.8 (7)
C12–N2–C13	103.3 (7)	N4–C14–C15	112.6 (6)
N4–N3–C8	109.3 (6)	O4–C17–C16	123.8 (7)
N3–N4–C14	114.9 (5)	O4–C17–C18	117.1 (7)
O1–C1–C2	129.2 (7)	O5–C18–C17	123.5 (6)
O1–C1–C6	109.0 (6)	O5–C18–C19	116.9 (7)
O2–C6–C5	128.4 (6)	O6–C19–C18	114.3 (6)
O2–C6–C1	110.8 (6)	O6–C19–C20	125.2 (6)
O1–C7–O2	108.4 (6)		

Antifungal activity of the target oximino esters **5a-r**

The antifungal activity of the synthesized oximino esters **5a-r** is presented in Table 4. Compounds **5a**, **5g**, **5j**, **5l**, and **5m** showed the best antifungal activity against the tested *Candida albicans* strain in the DIZ assay with DIZ value of 15 mm being about 1.2-fold less potent than fluconazole. Whereas, compounds **5a**, **5b**, **5d-f**, and **5k-r** were the most active oximino esters against the tested *Candida tropicalis* strain in the DIZ assay with DIZ values equal to or more than

Figure 1 ORTEP diagram of compound **5o**.

Note: Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

Abbreviation: ORTEP, Oak Ridge Thermal-Ellipsoid Plot Program.

Table 3 Hydrogen-bond geometry (Å, °) of compound **5o**

D–H ...A	D–H	H ...A	D ...A	D–H ...A
C3–H3A ...N2 ⁱ	0.9300	2.5400	3.420 (10)	157.00
C10–H10B ...O3 ⁱⁱ	0.9700	2.6000	3.435 (9)	145.00
C21–H21A ...O1 ⁱⁱⁱ	0.9600	2.4600	3.406 (9)	169.00

Notes: Symmetry codes: (i) $-x+2, -y, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $x, y+1, z+1$.

20 mm being nearly equipotent with fluconazole. Regarding the tested *Candida parapsilosis* and *Aspergillus niger* strains, compounds **5a–r** displayed moderate activity in the DIZ assay with DIZ values ranging from 11 to 23 mm, being nearly equipotent with fluconazole. Moreover, compounds **5l** and **5m** (bearing trifluoromethylphenyl moiety) were the most active equipotent congeners in the MIC assay against the tested *C. albicans* strain with MIC value of 0.148 $\mu\text{mol/mL}$, being about threefold less potent than fluconazole whereas, compound **5b**, bearing the 4-bromophenyl fragment, was the most active oximino ester toward *C. tropicalis* with MIC value of 0.289 $\mu\text{mol/mL}$, being about six times less potent than fluconazole, followed by the equipotent candidates **5l** and **5m** which displayed MIC value of 0.297 $\mu\text{mol/mL}$. Compound **5o** incorporating 3,4,5-trimethoxyphenyl moiety exhibited the best activity against the tested *C. parapsilosis* with MIC value of 0.141 $\mu\text{mol/mL}$, being nearly threefold less potent than fluconazole. The oximino ester **5l** was

the most active anti-*A. niger* compound with MIC value of 0.297 $\mu\text{mol/mL}$, being equipotent with compound **5m**. Furthermore, compounds **5h**, **5i**, **5n**, and **5q** manifested the weakest antifungal activity among the synthesized oximino esters **5a–r** toward *C. tropicalis*, *C. parapsilosis*, *C. albicans*, and *A. niger*, respectively, with MIC values equal to or more than 1.18 $\mu\text{mol/mL}$. In summary, it seems that substitution with the 3- or 4-trifluoromethyl moiety (compounds **5l** and **5m**) is favored for the antifungal potential of the prepared oximino esters **5a–r**, particularly toward *C. albicans* and *A. niger*. On the other hand, the best anti-*C. tropicalis* and anti-*C. parapsilosis* activity was achieved with 4-bromophenyl (compound **5b**) and 3,4,5-trimethoxyphenyl (compound **5o**) moieties, respectively. Regarding the heteroaryl-bearing oximino esters (compounds **5p–r**), the thiophene-bearing compound **5r** is the best heteroaryl-bearing oximino ester against both *C. tropicalis* (MIC value = 0.347 $\mu\text{mol/mL}$) and *A. niger* (MIC value = 0.693 $\mu\text{mol/mL}$), and the pyridine-bearing compound, **5p**, is the best heteroaryl-bearing oximino ester against *C. parapsilosis* (MIC value = 0.176 $\mu\text{mol/mL}$). The weak to moderate antifungal activity of the synthesized compounds **5a–r** as compared to the reference antifungal drugs might be attributed to either their poor pharmacokinetic properties or improper interaction with their target fungal protein.

Figure 2 Molecular packing of compound **5o** enables the viewing of hydrogen bonds which are drawn as dashed lines along *b* axis.

Table 4 Antifungal potential of the target oximino esters **5a-r** against *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *A. niger*

Compound no	<i>Candida albicans</i>		<i>Candida tropicalis</i>		<i>Candida parapsilosis</i>		<i>Aspergillus niger</i>	
	DIZ $\pm$ SD ^a (mm)	MIC (μ mol/mL)	DIZ $\pm$ SD ^a (mm)	MIC (μ mol/mL)	DIZ $\pm$ SD ^a (mm)	MIC (μ mol/mL)	DIZ $\pm$ SD ^a (mm)	MIC (μ mol/mL)
5a	15 $\pm$ 0.60	0.705	22 $\pm$ 0.40	0.352	19 $\pm$ 0.58	0.352	14 $\pm$ 0.58	0.705
5b	14 $\pm$ 0.40	0.579	20 $\pm$ 0.30	0.289	18 $\pm$ 0.20	0.145	15 $\pm$ 1.20	0.579
5c	9 $\pm$ 0.20	0.322	17 $\pm$ 0.50	0.644	13 $\pm$ 0.50	> 1.29	13 $\pm$ 0.40	0.644
5d	13 $\pm$ 0.40	0.644	21 $\pm$ 1.00	0.322	19 $\pm$ 1.00	0.161	13 $\pm$ 0.50	0.644
5e	13 $\pm$ 0.58	0.322	21 $\pm$ 0.50	0.644	18 $\pm$ 0.58	0.322	11 $\pm$ 0.40	1.29
5f	14 $\pm$ 0.30	0.671	22 $\pm$ 0.60	0.336	17 $\pm$ 1.00	0.336	13 $\pm$ 0.60	0.671
5g	15 $\pm$ 0.50	0.168	9 $\pm$ 0.50	0.336	19 $\pm$ 0.58	0.336	23 $\pm$ 0.80	0.336
5h	13 $\pm$ 0.43	0.651	19 $\pm$ 1.00	> 1.30	18 $\pm$ 0.20	0.163	13 $\pm$ 0.50	0.651
5i	13 $\pm$ 0.58	0.678	14 $\pm$ 0.58	0.678	11 $\pm$ 0.20	> 1.36	16 $\pm$ 0.12	0.678
5j	15 $\pm$ 0.50	0.339	19 $\pm$ 0.50	0.678	19 $\pm$ 0.58	0.170	17 $\pm$ 0.80	0.678
5k	14 $\pm$ 1.10	0.678	22 $\pm$ 0.80	0.339	19 $\pm$ 1.00	0.339	15 $\pm$ 0.90	0.678
5l	15 $\pm$ 0.90	0.148	20 $\pm$ 0.40	0.297	17 $\pm$ 0.58	0.148	23 $\pm$ 0.40	0.297
5m	15 $\pm$ 0.58	0.148	21 $\pm$ 1.00	0.297	12 $\pm$ 0.10	0.148	23 $\pm$ 1.10	0.297
5n	13 $\pm$ 1.00	1.18	22 $\pm$ 0.40	0.592	20 $\pm$ 0.40	1.18	14 $\pm$ 0.40	0.592
5o	12 $\pm$ 0.43	0.565	21 $\pm$ 0.50	0.565	19 $\pm$ 0.58	0.141	15 $\pm$ 0.60	0.565
5p	14 $\pm$ 1.10	0.703	21 $\pm$ 1.00	0.351	17 $\pm$ 0.80	0.176	14 $\pm$ 0.50	0.703
5q	13 $\pm$ 0.60	0.693	21 $\pm$ 0.50	0.347	20 $\pm$ 0.50	0.693	12 $\pm$ 0.43	1.39
5r	13 $\pm$ 0.58	0.693	20 $\pm$ 0.50	0.347	19 $\pm$ 0.50	0.693	18 $\pm$ 0.20	0.693
Fluconazole	18 $\pm$ 1.10	0.051	19 $\pm$ 1.00	0.045	19 $\pm$ 0.90	0.047	ND	ND
Ketoconazole	ND	ND	ND	ND	ND	ND	29 $\pm$ 0.60	0.02

Note: ^aThe arithmetic mean of the inhibition zone diameters in mean $\pm$ SD.

Abbreviations: DIZ, diameter of the inhibition zone; MIC, minimum inhibitory concentration; ND, not determined.

Conclusion

The synthesis and spectroscopic identification of certain new oximino esters **5a-r** bearing imidazole and 1,3-benzodioxole fragments have been reported. Single-crystal X-ray analysis of compound **5o** confirmed without doubt the assigned chemical structures of the title compounds as well as confirmed the (*E*)-configuration of their oximino group. The antifungal potentials of the title compounds **5a-r** have been examined in vitro against four fungal strains using DIZ and MIC assays. It seems that substitution with the 3- or 4-trifluoromethyl moiety (compounds **5l** and **5m**) is favored for the antifungal potential of the prepared oximino esters **5a-r**, particularly toward *C. albicans* and *A. niger*. On the other hand, the best anti-*C. tropicalis* and anti-*C. parapsilosis* activity was achieved with 4-bromophenyl (compound **5b**) and 3,4,5-trimethoxyphenyl (compound **5o**) moieties, respectively. The results of the current investigation could support the development of new antifungal lead candidates.

Supporting materials

The details of the experimental methods which were adopted for the antifungal evaluation of the prepared compounds and representative NMR spectra (Figures S1–S6) of the target compounds are provided as Supplementary materials.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Antifungal activity

Materials

The reference standard antifungal drug, ketoconazole, was purchased from Sigma-Aldrich Co. (St Louis, MO, USA). Liquid RPMI 1640 medium supplemented with L-glutamine was obtained from Gibco-BRL, Life Technologies (Paisley, Scotland). Sabouraud Dextrose Agar (SDA) was obtained from Merck Co. (Darmstadt, Germany). Dimethyl sulfoxide (100%) was used to dissolve ketoconazole, and/or the tested compound 4 to give an initial concentration of 2,048 mg/L.

Organisms

The used fungal strains are *Candida albicans* (ATCC 90028), *Candida tropicalis* (ATCC 66029), *Candida parapsilosis* (ATCC 22019) and *Aspergillus niger* (ATCC 16404).

Preparation of fungal inocula

The inocula of the standard mold *Aspergillus niger* strain have been prepared by removing the sporulated *A. niger* from the Sabouraud Dextrose agar slant with a microbiological loop and the spores have been suspended in 10 mL of sterile water. The suspension has been filtered through sterile gauze to remove hyphae. The resulting suspension of conidia has been vigorously mixed using a vortex. The suspension has been adjusted to 1×10^5 CFU/mL using spectrophotometer. This fungal suspension has been diluted 1:5 with RPMI medium to obtain suspensions having 2× of the required final concentration. This conidial suspension had a final concentration of 1×10^4 CFU/mL when mixed with the tested solution of compound 4. On the other hand, the inocula of the standard yeast strains of *C. albicans*, *C. tropicalis* and *C. parapsilosis* have been prepared by suspending five representative colonies, obtained from 24 to 48 h culture on Sabouraud Dextrose agar medium, in sterile distilled water. The final inoculum concentration must be between 0.5×10^5 and 2.5×10^5 CFU/mL.

Preparation of the tested compound solution

Briefly, a twofold dilution series of the tested compounds has been prepared in a double strength RPMI 1640 culture medium. Ten serial dilutions were prepared to give concentrations ranged from 1,024 mg/L to 2 mg/L.

Antifungal susceptibility studies

Minimum Inhibitory Concentrations (MICs) have been determined by broth microdilution testing as described previously by EUCAST.¹ The experiment was carried out in duplicate. Briefly, one mL of RPMI 1640 medium from each of the bottle containing the corresponding concentration of the tested

compounds has been transferred into sterile 7 mL Sterilin tubes (Thermo Fisher Scientific, Waltham, MA, USA). The RPMI 1640 medium containing 1,024 mg/L of the tested compounds has been dispensed to tube 1, the medium containing 512 mg/L has been dispensed to tube 2, the medium containing 256 mg/L has been dispensed to tube 3 and so on to tube 10 for the medium containing 2 mg/L of the tested compounds. One mL of the medium has been dispensed in tubes 11 (positive control) and 12 (negative control). One mL of the diluted inoculum suspension has transferred to each tube except tube 12 to bring the tested compounds dilutions to the required final test concentrations. The tubes were incubated at 35°C for 72 h. The MICs of the tested compounds were determined visually by recording the degree of growth inhibition in each tube. The microanalysis results (Table S1) of the target compounds **5a-r** agreed favorably with the proposed structures within $\pm 0.4\%$ of the theoretical values.

Table S1 Microanalysis data of the title compounds **5a-r**

Compound no	Elemental analysis		
	C	H	N
5a	Calcd.: 66.11 Found: 66.34	Calcd.: 4.72 Found: 4.53	Calcd.: 11.56 Found: 11.26
5b	Calcd.: 54.31 Found: 54.65	Calcd.: 3.65 Found: 3.84	Calcd.: 9.50 Found: 9.42
5c	Calcd.: 60.38 Found: 59.99	Calcd.: 4.05 Found: 4.15	Calcd.: 10.56 Found: 10.36
5d	Calcd.: 60.38 Found: 60.72	Calcd.: 4.05 Found: 4.41	Calcd.: 10.56 Found: 10.22
5e	Calcd.: 60.38 Found: 60.11	Calcd.: 4.05 Found: 3.75	Calcd.: 10.56 Found: 10.84
5f	Calcd.: 62.99 Found: 62.76	Calcd.: 4.23 Found: 3.98	Calcd.: 11.02 Found: 11.28
5g	Calcd.: 62.99 Found: 62.83	Calcd.: 4.23 Found: 4.16	Calcd.: 11.02 Found: 11.09
5h	Calcd.: 64.12 Found: 66.86	Calcd.: 4.87 Found: 4.69	Calcd.: 10.68 Found: 10.97
5i	Calcd.: 66.83 Found: 66.69	Calcd.: 5.07 Found: 4.99	Calcd.: 11.13 Found: 10.89
5j	Calcd.: 66.83 Found: 67.01	Calcd.: 5.07 Found: 5.33	Calcd.: 11.13 Found: 11.46
5k	Calcd.: 66.83 Found: 66.54	Calcd.: 5.07 Found: 4.78	Calcd.: 11.13 Found: 11.49
5l	Calcd.: 58.47 Found: 58.26	Calcd.: 3.74 Found: 3.64	Calcd.: 9.74 Found: 9.44
5m	Calcd.: 58.47 Found: 58.74	Calcd.: 3.74 Found: 3.36	Calcd.: 9.74 Found: 9.98
5n	Calcd.: 55.57 Found: 55.89	Calcd.: 3.50 Found: 3.63	Calcd.: 9.72 Found: 9.43
5o	Calcd.: 60.92 Found: 60.69	Calcd.: 5.11 Found: 4.96	Calcd.: 9.27 Found: 9.56
5p	Calcd.: 62.63 Found: 62.96	Calcd.: 4.43 Found: 4.08	Calcd.: 15.38 Found: 15.76
5q	Calcd.: 58.53 Found: 56.32	Calcd.: 4.09 Found: 4.47	Calcd.: 11.38 Found: 11.19
5r	Calcd.: 58.53 Found: 58.69	Calcd.: 4.09 Found: 3.99	Calcd.: 11.38 Found: 11.68

PROTON CDCl₃ D:\ abari 2 Figure S1 ¹H NMR spectrum of compound 5d.C13CPD CDCl₃ D:\ abari 2 Figure S2 ¹³C NMR spectrum of compound 5d.

PROTON CDCl₃ D:\ abari 1 Figure S3 ¹H NMR spectrum of compound 5e.C13CPD CDCl₃ D:\ abari 1 Figure S4 ¹³C NMR spectrum of compound 5e.

Figure S5 ¹H NMR spectrum of compound 5k. Figure S6 ¹³C NMR spectrum of compound 5k.

Reference

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