Full Paper

3-Imidazolyl-Substituted Flavans as Potential Antifungal Agents: Synthesis, Stereochemical Properties, and Antifungal Activity

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A new series of 3-imidazolyl-substituted flavan derivatives being equipped with a *N*-(phenethyl)-azole scaffold as the common pharmacophore of azole antifungals, were synthesized. The stereochemical and conformational properties of compounds were also characterized by ^{1}H-NMR data. The results of the antifungal evaluation of *trans*-3-imidazolyl-substituted flavan-4-ones and (*Z*)-*trans*-3-imidazolyl-substituted flavan-4-one oximes in comparison with the reference drug fluconazole indicated that most target compounds possessed significant *in-vitro* antifungal activities against the tested fungi, comparable or superior to fluconazole.

Keywords: Antifungal activity / Azole antifungals / Favan-4-one / Imidazole / Oxime

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Introduction

During the past three decades, the incidence of both community-acquired and nosocomial fungal infections has increased dramatically. Life-threatening fungal infections have emerged as important causes of morbidity and mortality in patients that become severely immunocompromised because of underlying diseases such as leukemia and AIDS or patients, who undergo cancer chemotherapy and organ- or bone-marrow transplantation. A major problem in the treatment of fungal infections is the spread of drug resistance mainly in patients that are subjected to chronological therapy with antifungal agents, i.e. those treated with broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs [1, 2]. Moreover, the current antifungal therapy suffers from drug-related toxicity, non-optimal pharmacokinetics, and serious drug-drug interactions. Therefore, new chemotherapeutic agents with higher efficiency, broader spectrum, and lower toxicity useful for treating widespread fungal infections are urgently needed [3].

The common antifungal agents currently used in clinic fall into six major classes: azoles, polyenes, echinocandins, allylamines, thiocarbamates, and fluoropyrimidines [4, 5]. Among these classes, azoles represent one of the largest classes of antifungal agents with fungistatic, orally active, and broad-spectrum activities against most yeasts and filamentous fungi. They are widely used in antifungal chemotherapy and still remain viable lead structures in the search of a more efficacious, broad spectrum, and systemic antifungal drug [6, 7]. The azole antifungals are *N*-substituted imidazoles or 1,2,4-triazoles that inhibit the fungal cytochrome P450-dependent 14α-lanosterol demethylase, which catalyzes the removal of the 14-methyl group of lanosterol through three successive monooxygenation reactions in the fungal ergosterol biosynthesis pathway [3]. The drugs bind through a nitrogen group in their 5-membered azole ring to the heme group in the target protein and block 14-demethylation of lanosterol, leading to substitution of methylated ster-

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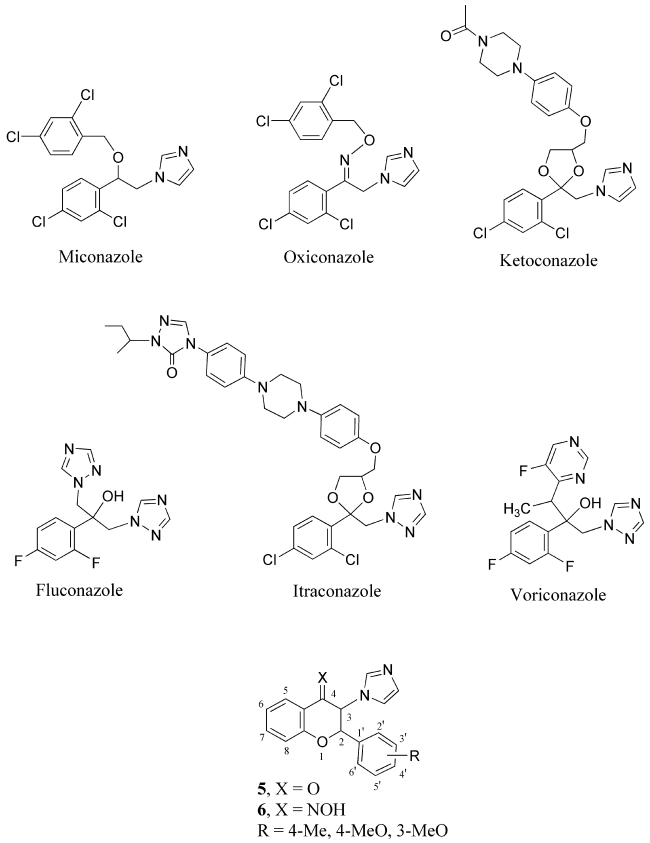
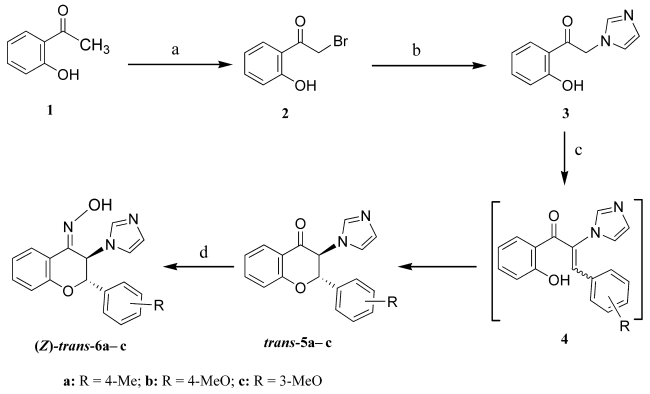


Figure 1. Chemical structures of some clinically important azole antifungals and the designed compounds **5** and **6**, bearing a *N*-(phenethyl)azole scaffold as common pharmacophore of the azole antifungals.

ols in the membrane and depletion of ergosterol. The result is an accumulation of precursors with abnormalities in the fungal membrane permeability and membrane-bound enzyme activity. Although 14α-demethylase is also involved in mammalian cholesterol synthesis, azoles are therapeutic because they have a significantly higher affinity for the fungal cytochrome P-450 enzyme than the human cytochrome P-450 enzyme [8, 9].

A survey among the chemical structures of azole antifungals such as miconazole, oxiconazole, ketoconazole, fluconazole, itraconazole, and voriconazole (Fig. 1) [5, 7] reveals in all of these molecules the presence of one common pharmacophoric portion, which is characterized by a phenyl ring linked by an ethane chain to a nitrogen of imidazole or 1,2,4-triazole ring [*N*-(phenethyl)azole backbone]. In the research field of azole antifungal agents, investigations with a chroman core have been reported by us [10 – 12]. In relation to these works, we synthesized new 3-imidazolyl-substituted flavan derivatives, which consisted of a *N*-(phenethyl)azole scaffold as the common pharmacophore of azole antifungals. Thus, we report



Reagents and conditions: (a) $CuBr_2$, $CHCl_3$ / EtOAc (1 : 1), reflux, 5 h, 94%; (b) imidazole excess, DMF, 40 – 45°C, 5 h, 45%; (c) benzaldehyde derivatives, piperidine, 2-propanol, reflux, 4 to 6 h, yield: 70 – 85%; (d) $HONH_2$ 6 · HCl, K_2CO_3, MeOH, rt., yield: 67-87%.

Scheme 1. Synthesis of *trans*-**5** and (*Z*)-*trans*-**6**.

here the synthesis, stereochemical properties, and antifungal activity of 3-imidazolyl-substituted flavan derivatives **5** and **6** (Fig. 1).

Results and discussion

Chemistry

Our synthetic pathway to target compounds is illustrated in Scheme 1. The starting 2-hydroxyacetophenone **1** was brominated with copper (II) bromide in refluxing $CHCl_3$ / AcOEt to give corresponding α-bromoketone **2**. Reaction of imidazole with α-bromoketone **2** in DMF, at 40 – 45°C afforded 1-(2-hydroxyphenyl)-2-(imidazol-1-yl)ethanone **3** [13]. Flavanones are commonly synthesized via the Claisen – Schmidt condensation between 2-hydroxyacetophenone and a benzaldehyde and subsequent intramolecular Michael addition of the 2′-hydroxychalcone intermediate. Commonly, both reactions are catalyzed by acids or bases in homogeneous media [14]. Thus, the base-catalyzed reaction of 1-(2-hydroxyphenyl)-2-(imidazol-1-yl)ethanone **3** and methyl- or methoxybenzaldehyde using piperidine in refluxing 2-propanol gave the desired *trans*-3-imidazolylflavanone derivatives **5a – c**. The configuration of the 2-aryl group and the 3-imidazole ring was assigned as *trans* by the large vicinal coupling constant between C2- and C3-protons ($J_{2,3}$ = 12.5 Hz). The ketones **5a – c** were stereoselectively converted to the pure (*Z*)-oximes **6a – c** by stirring with excess of hydroxylamine hydrochloride (three equivalents) in the presence of K_2CO_3 in methanol at room temperature. The geometry of the oximes **6a – c** was elucidated by ^{1}H-NMR spectroscopy [15]. In particular, this configurational assignment was based on the deshielding effect of the oxime oxygen

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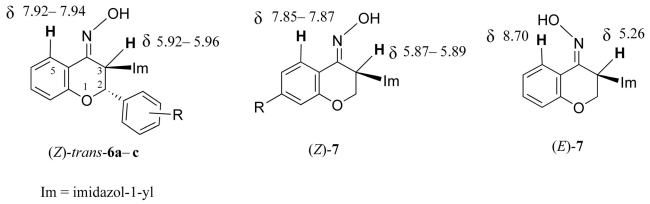
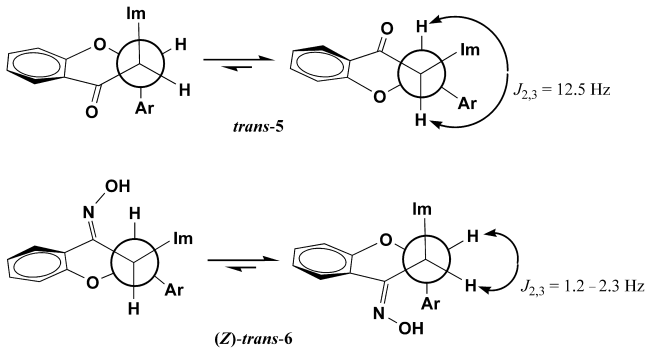


^{1}H-NMR chemical shifts of the C-3 and C-5 protons of compounds (*Z*)-*trans*-**6a-c** and structurally related compounds (*Z*)- and (*E*)-**7** was used for this characterization [11].

Figure 2. Assignment of the oxime geometry as (*Z*)-configuration in compounds *trans*-**6a – c**.



(Im = imidazol-1-yl; Ar = substituted phenyl).

Figure 3. Comparison of the 2,3-coupling constants ($J_{2,3}$) of *trans*-flavanones **5a-c** and (*Z*)-*trans*-flavanone oximes **6a – c** pointing out the remarkable differences between the preferential conformations of these compounds.

on the C-3 proton in the (*Z*)-oxime and on the C-5 proton in the (*E*)-oxime of the chroman ring [10 – 12]. The comparison of ^{1}H-NMR chemical shifts of the C-3 and C-5 protons in compounds **6a – c** and the structurally related (*E*)- and (*Z*)-chromanone oximes **7** [11] revealed that the chemical shifts of compounds **6a – c** to be virtually the same as that of compound (*Z*)-**7** (Fig. 2). Thus, the stereochemistry of the oxime moiety of compounds **6a – c** was assigned to be of (*Z*)-geometry.

In addition, the resulting ^{1}H-NMR data of flavanones **5a – c** and flavanone oximes **6a – c** reveal conformational aspects of these compounds and their dissimilarities. By comparison of the 2,3-coupling constants ($J_{2,3}$) of flavanones **5a – c** and flavanone oximes **6a – c**, it can be seen that formation of oximes results in a remarkable decrease in the vicinal coupling constants of the flavan ring (Fig. 3). These results suggest that the dihedral angle between H – C(2) and H – C(3) in the flavanone oximes **6a – c** is small. Thus, the relatively larg 2,3-coupling constant ($J_{2,3}$ = 12.5 Hz) in flavanones **5a – c** confirms the preferred pseudo-axial conformation of H-2 and H-3. The small 2,3-coupling constant ($J_{2,3}$ = 1.2 – 2.3 Hz) in flavanone oximes **6a – c** suggests a preference for the conformation in which H-2 and H-3 are in pseudo-equatorial orientation (Fig. 3).

All described compounds, flavanones **5a – c** and flavanone oximes **6a – c**, which possess two chiral centers in their flavan ring at the C-2 and C-3 positions, are racemates.

Antifungal activity

The *in-vitro* antifungal activities of the synthesized compounds **5a – c** and **6a – c** were investigated against several representative pathogenic fungi as yeast (*Candida albicans* and *Saccharomyces cerevisiae*), a dermatophyte (*Microsporum gypseum*), and a mould (*Aspergillus niger*) (Table 1) using the agar-dilution method [16]. The MIC (minimum inhibitory concentration) values were determined by comparison to fluconazole as reference drug. In general, the MIC values of the test compounds indicate that both flavanones **5a – c** and flavanone oximes **6a – c** were active against all fungi tested (MIC ≤ 32 μg/mL). Among them, 4′-methoxyflavanone oxime derivative **6b** was the most potent against *C. albicans*, with a MIC value of 4 μg/mL. In addition, the activity of this compound against *C. albicans* was comparable or superior to that of the reference drug fluconazole (MIC = 8 μg/mL). Compound **6c** was equipotent in anti-*Candida* activity with respect to fluconazole with a MIC value of 8 μg/mL. The remaining compounds **5a – c** and **6a** exhibited equipotent activity against *C. albicans* (MIC = 16 μg/mL).

The growth-inhibitory activities of the target compound against *S. cerevisiae* demonstrate that all compounds possessed a comparable or better activity with respect to fluconazole. Moreover, between flavanones **5a – c** and flavanone oximes **6a – c** there was no appreciable difference with regard to the activity against this microorganism with the exception of **5a** which was slightly less active than its oxime analog. All compounds possessed a comparable or better activity against *A. niger* (MIC ≤ 32 μg/mL) compared to fluconazole. Among the compounds tested, 4′-methoxyflavanone **5b** and 4′-methylflavanone oxime **6a** showed the highest activity against *A. niger*, and their MIC values were determined to be 8 μg/mL. Their growth inhibitory activities were fourfold more potent than that of fluconazole. Furthermore, all compounds also inhibited the growth of *M. gypseum* (MIC ≤ 16 μg/mL) more significantly than fluconazole. 3′-Methoxyflavanone oxime **6c** was superior in inhibiting the growth of *M. gypseum* (MIC = 2 μg/mL), being 16 times more potent than fluconazole.

The antifungal data of this limited series of compounds revealed that the type and position of the substituent on the 2-phenyl ring and the functional group linked to the 4-position of the flavan ring seemed to have

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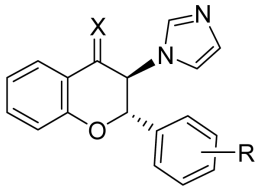
Table 1. *In-vitro* antifungal activity of compounds **5a – c** and **6a – c**.



Compounds	X	R	*C. albicans* (PTCC 5027)	*S. cerevisiae* (PTCC 5177)	*A. niger* (PTCC 5012)	*M. gypseum* (PTCC 5070)
5a	O	4-Me	16	32	32	8
5b	O	4-MeO	16	16	8	8
5c	O	3-MeO	16	16	16	16
(Z)-6a	NOH	4-Me	16	16	8	8
(Z)-6b	NOH	4-MeO	4	16	16	4
(Z)-6c	NOH	3-MeO	8	16	32	2
Fluconazole			8	32	32	32

(MICs in μg/mL)

varying influence on the antifungal activity against various fungi strains.

In conclusion, a series of new *trans*-3-imidazolyl flavans containing a 4-oxo or (*Z*)-4-hydroxyimino functional groups on the flavan ring were synthesized chemo- and streoselectively, as potential antifungal agents. The stereochemical and conformational properties of the compounds were also characterized by ^{1}H-NMR data. The results of the antifungal evaluation of the test compounds in comparison to the reference drug fluconazole indicated that most target compounds possessed significant *in-vitro* antifungal activities against the tested fungi, comparable or superior to fluconazole.

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The authors have declared no conflict of interest.

Experimental

Chemistry

Chemical reagents and all solvents used in this study were purchased from Merck Chemicals (Merck India). The 1-(2-hydroxyphenyl)-2-(imidazol-1-yl)ethanone **3** was prepared according to the literature method [11, 13]. Melting points were determined in open glass capillaries using a Bibby Stuart Scientific SMP3 apparatus (Bibby Scientific Ltd., Stone UK) and are uncorrected. NMR spectra were recorded using a Bruker 500 spectrometer (Bruker Bioscience, USA), and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. Elemental analyses were carried out on a HERAEUS CHN-O rapid elemental analyzer (Heraeus GmbH, Hanau, Germany) for C, H, and N, and the results are within ± 0.4% of the theoretical values. Merck silica gel 60 F254 plates were used for analytical TLC.

*General procedure for the synthesis of trans-3-(imidazol-1-yl)flavan-4-ones **5a – c***

A solution of 1-(2-hydroxyphenyl)-2-(imidazol-1-yl)ethanone **3** (3.0 mmol) and substituted bezaldehyde (3.15 mmol) in 2-propanol (3 mL) containing piperidine (1.0 mmol) was refluxed until the compound **3** was consumed (4 to 6 h). The reaction mixture was cooled and agitated for 24 to 48 h in the fridge. To the cold solution of reaction mixture was added diethyl ether. The crystalline product **5a – c** was filtered off, washed with cold 2-propanol, and diethyl ether.

*(±)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(4-methylphenyl)-4H-1-benzopyran-4-one **5a***

Yield: 70%; m.p.: 203 – 204°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 6.09 (d, *J* = 12.55 Hz, 1H, H-2), 6.22 (d, *J* = 12.51 Hz, 1H, H-3), 6.81 (br s, 1H, imidazole H-5), 7.05 – 7.24 (m, 5H, H-6, H-8, H-3′, H-5′ and imidazole H-4), 7.34 (d, *J* = 7.62 Hz, 2H, H-2′ and H-6′), 7.54 (br s, 1H, imidazole H-2), 7.69 (t, *J* = 7.31 Hz, 1H, H-7), 7.88 (d, *J* = 7.52 Hz, 1H, H-5); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 21.66, 64.09, 82.37, 118.87, 120.06, 120.62, 123.06, 127.91, 128.531, 128.71, 129.83, 133.54, 137.87, 139.49, 161.61, 189.69. Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.73; H, 5.44; N, 9.08.

*(±)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one **5b***

Yield: 85%; m.p.: 196 – 197°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.74 (s, 3H, OCH_3), 6.05 (d, *J* = 12.53 Hz, 1H, H-3), 6.17 (d, *J* = 12.51 Hz, 1H, H-2), 6.82 (br s, 1H, imidazole H-5), 6.89 (d, *J* = 8.36 Hz, 2H, H-3′ and H-5′), 7.16 (d, *J* = 8.27 Hz, 1H, H-8), 7.18 (br s, 1H, imidazole H-4), 7.21 (t, *J* = 7.50 Hz, 1H, H-6), 7.38 (d, *J* = 8.29 Hz, 2H, H-2′ and H-6′), 7.44 (br s, 1H, imidazole H-2), 7.69 (dt, *J* = 7.70 and 1.33 Hz,

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1H, H-7), 7.88 (d, *J* = 7.26 and 1.02 Hz, 1H, H-5); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 55.96, 64.04, 82.26, 114.61, 118.87, 120.65, 123.00, 127.91, 128.53. 129.99, 137.82, 160.60, 161.66, 189.86. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.23; H, 5.00; N, 8.69.

(±)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(3-methoxyphenyl)-4H-1-benzopyran-4-one ***5c***

Yield: 81%; m.p.: 168 – 169°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.72 (s, 3H, OCH_3), 6.07 (d, *J* = 12.46 Hz, 1H, H-2), 6.17 (d, *J* = 12.45 Hz, 1H, H-3), 6.85 (br s, 1H, imidazole H-5), 6.90 (d, *J* = 8.10 Hz, 1H, H-4′), 6.98 (d, *J* = 7.35 Hz, 1H, H-6′), 7.02 (s, 1H, H-2′), 7.08 – 7.30 (m, 4H, H-6, H-8, H-5′ and imidazole H-4), 7.48 (br s, 1H, imidazole H-2), 7.71 (t, *J* = 7.72 Hz, 1H, H-7), 7.90 (d, *J* = 7.72 Hz, 1H, H-5); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 55.98, 64.11, 82.43, 113.92, 115.54, 118.89, 120.64, 120.72, 123.12, 127.92, 130.39, 137.88, 137.99, 159.95, 161.53, 189.63. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.36; H, 4.91; N, 8.74.

*General procedure for the synthesis of trans-3-(imidazol-1-yl)flavan-4-one (Z)-***oximes** ***6a – c***

A mixture of *trans*-3-imidazolylflavanone **5a – c** (1.0 mmol), hydroxylamine hydrochloride (3 mmol) and K_2CO_3 (1.0 mmol) in methanol (4 mL) was stirred at room temperature for three to six days. The reaction mixture was poured into water, and the precipitate was filtered, washed with water, and crystallized from methanol to afford pure (*Z*)-isomer of **6a – c**.

(±)-(Z)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(4-methylphenyl)-4H-1-benzopyran-4-one oxime ***6a***

Yield: 69%; m.p.: 204 – 205°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 5.55 (d, *J* = 2.30 Hz, 1H, H-2), 5.95 (d, *J* = 2.39 Hz, 1H, H-3), 6.65 (s, 1H, imidazole H-5), 6.72 (s, 1H, imidazole H-4), 7.05-7.19 (m, 7H, H-2′, H-3′, H-5′, H-6′, H-6, H-8 and imidazole H-2), 7.43 (t, *J* = 7.08 Hz, 1H, H-7), 7.94 (dd, *J* = 7.86 and 1.24 Hz, 1H, H-5), 11.92 (s, 1H, oxime); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 21.59, 51.57, 79.53, 118.74, 118.94, 119.35, 123.47, 124.40, 126.64, 128.85, 129.54, 132.12, 133.65, 138.11, 138.41, 146.42, 155.97. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.79; H, 5.39; N, 13.15.

(±)-(Z)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one oxime ***6b***

Yield: 87%; m.p.: 184 – 186°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.70 (s, 3H, OCH_3), 5.53 (br s, 1H, H-2), 5.92 (br s, 1H, H-3), 6.66 (br s, 1H, imidazole H-5), 6.72 (br s, 1H, imidazole H-4), 6.81 (d, *J* = 7.50 Hz, 2H, H-3′ and H-5′), 7.04 – 7.37 (m, 5H, H-2′, H-6′, H-6, H-8 and imidazole H-2), 7.42 (t, *J* = 7.50 Hz, 1H, H-7), 7.92 (d, *J* = 7.50 Hz, 1H, H-5), 11.92 (s, 1H, oxime); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 54.99, 78.43, 113.46, 114.16, 117.83, 118.06, 122.58, 123.50, 127.20, 127.62, 127.81, 131.22, 145.54, 155.15, 158.96. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.92; H, 5.19; N, 12.52.

(±)-(Z)-trans-2,3-Dihydro-3-(1H-imidazol-1-yl)-2-(3-methoxyphenyl)-4H-1-benzopyran-4-one oxime ***6c***

Yield: 67%; m.p.: 229 – 230°C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.64 (s, 3H, OCH_3), 5.54 (d, *J* = 1.20 Hz, 1H, H-2), 5.96 (d, *J* = 1.18 Hz, 1H, H-3), 6.65 (br s, 1H, imidazole H-5), 6.70 (br s, 2H, H-2′ and imidazole H-4), 6.81 (m, 2H, H-5′ and H-6), 7.09 – 7.21 (m, 4H, H-4′, H-6′, H-8 and imidazole H-2), 7.43 (dt, *J* = 7.75 and 1.5 Hz, 1H, H-7), 7.93 (dd, *J* = 8.00 and 1.0 Hz, 1H, H-5), 11.94 (s, 1H, oxime); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 50.81, 54.93, 78.56, 111.14, 113.89, 117.91, 118.13, 122.68, 123.51, 129.19, 131.27, 137.22, 145.40, 154.98, 158.96. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.22; H, 5.09; N, 12.71.

Antifungal activity

The minimum inhibitory concentrations (MICs) were determined by the agar dilution method against the pathogenic fungi *Candida albicans, Saccharomyces cerevisiae, Aspergillus niger*, and *Microsporum gypseum* [16]. Sabouraud dextrose agar (SDA) was employed for fungal growth. Stock solutions of tested compounds were prepared in dimethyl sulfoxide (DMSO). Inocula containing approximately 10^5 CFUs/mL of fungi were prepared from broth cultures in log-phase growth. Fungal plates were made in triplicate and incubated at 30°C about 24 to 48 h for yeast, about 72 h for moulds, and about 168 h for dermatophytes. The MIC value was defined as the lowest concentration of the antifungal agent, at which no growth on the plate was visible; all experiments were repeated at least three times. To ensure that the solvent had no effect on fungal growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

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