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Short communication

Synthesis and antifungal activities of some aryl [3-(imidazol-1-yl/triazol-1-ylmethyl) benzofuran-2-yl] ketoximes

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Abstract

In this study, some aryl [3-(imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl] ketones, aryl (3-methyl-benzofuran-2-yl) ketoximes and aryl [3-(imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl] ketoximes were synthesised starting from 2-aryloyl-3-methyl-benzofuranes. The structure elucidation of the compounds was performed by IR, ^{1}H-NMR, MASS spectroscopy and elemental analyses. Antifungal activities of the compounds were examined and moderate activity was obtained.
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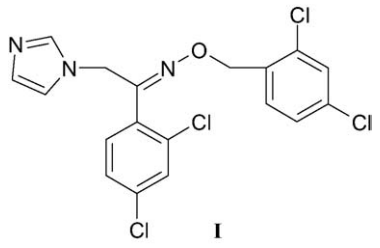
Keywords: Aryl [3-(imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl] ketoximes; Antifungal activity

1. Introduction

It is an irrefutable fact that, not only the increase in fungal infections but also the resistance gained to the currently used drugs in recent years directed the studies on obtaining new antifungal drugs. Present drugs' renal toxicity and drug–drug interactions they caused are also major features appealing the search for novel potent compounds [1]. Concerning this issue, after it was discovered that oxiconazole **I**, i.e. carrying both azole and oxime residue, is a very effective antifungal agent, oximes became of interest. Since then, a number of oximes [2–14] were synthesised and found to be active against fungi. Encouraged by the successful results obtained from these works, we planned to prepare series of diaryl ketoximes, in which one of the aryl residues was replaced with benzofuran in a bioisosteric approach and obtained significant antifungal activity, against *Candida albicans*, from our works on aryl benzofuryl ketoxime series [15,16]. Highly effective compounds of these works should be characterised as; aryl benzofuryl ketoximes, non-substituted or substituted with a small alkyl group on the oxime residue. On the other hand, even though azole antifungals constitute a large group in antifungal drugs, in our literature researches we could find only so few efforts [10,11,17,18] on combining this group with oximes. Furthermore, we consider it of high importance to obtain novel azoles as their widespread and prolonged use has led to the development of the multidrug resistance, possessing a major hurdle in antifungal therapy [19,20]. In this study, in continuation of our works on aryl benzofuryl ketoxime series, we aimed to combine our potent antifungal aryl (3-methyl-benzofuran-2-yl) ketoximes with an azole residue, i.e. a well known inhibitor of fungal growth by inhibiting ergosterol synthesis binding to the heme cofactor of the cytochrome CYP51 [21,22], with the above mentioned rationale and test the newly synthesised (3-methyl-benzofuran-2-yl) ketoxime's, 2-aryloyl-3-(1-imidazolyl or triazolylmethyl) benzofurane's and their ketoxime's antifungal activities.



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2. Chemistry

Aryl [3-(imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl] ketoxime derivatives were synthesised as outlined in the scheme. The ketones (**1**) were obtained in modified Rap-Störmer reaction condition [23]. Consequently, they were reacted with N-bromosuccinimide (NBS) for obtaining aryl [3-(bromomethyl)benzofuran-2-yl] ketone derivatives (**2**) and the latter with imidazole or triazole for obtaining aryl [3-(imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl] ketone derivatives (**3**). The aimed oxime derivatives, **4** and **5**, were obtained by reacting hydroxylamine hydrochloride with aryl (3-methyl-benzofuran-2-yl) ketones (**1**) and aryl [3-(imidazol-1-yl/triazol-1-ylmethyl) benzofuran-2-yl] ketones (**3**), respectively. As expected the presence of *E* and *Z* isomers of the oxime derivatives was confirmed by a thin layer chromatography and NMR spectral data. Beside the OH group of the oxime residue, methyl, methoxy and methylene groups belonging to the *E* and *Z* isomers of the oxime derivatives resonated as two peaks with the corresponding integral values. In the IR spectra C=C and C=N stretching bands, characteristic for all the compounds were obtained at 1510–1616 cm^{-1} region. Ketone's C=O and oxime's O–H bands were observed at 1638–1647 and at 3115–3272 cm^{-1} regions, respectively. All the protons resonated as expected in the NMR spectra. In the NMR spectra aliphatic protons resonated in two groups for methyl 2.12 and 2.15, methoxy 3.77 and 3.80 and methylene 5.28 and 5.42 ppm regions, respectively, confirming the presence of the *E* and *Z* isomers. Also, characteristic oxime OH peaks were obtained at 11.80 and 12.87 ppm in two groups.

3. Results and discussion

Antifungal activity tests were performed by macrobroth dilution method using *C. albicans* (NRRL Y-27077 and clinical isolate, Osmangazi University, Faculty of Medicine, Eskişehir, Turkey) and *Candida glabrata* (ATCC 36583) strains. Antifungal agent ketoconazole was used as control. The MIC value obtained for the control compound is 12.5 μg ml^{-1} for all *Candida* strains. The activities of the aimed oxime and azole residue bearing compounds range between 5–12.5 and 5–25 μg ml^{-1} against *C. glabrata* and *C. albicans*, respectively. In consideration of the results; in regard to the activities of the benzofuryl ketones **1** to benzofuryl ketoximes **4** and (azol-1-yl) methylbenzofuryl ketones **3** to (azol-1-yl)methylbenzofuryl ketoximes **5**, it is seen that furnishing the oxime residue to the ketones increases the activity almost up to two or four folds in most of the compounds. However, addition of the azole residue; in regard to the activities of the benzofuryl ketones **1** to (azol-1-yl)methylbenzofuryl ketones **3**, slightly increased some of the compound's activity. Uncooperatively, oxime azole combination; in regard to the activities of the benzofuryl ketoximes **4** to (azol-1-yl)methylbenzofuryl ketoximes **5**, was not worked and the most active compounds appeared to be ketoximes **4**. Although, it is known that failure rate of combination of antifungal agents with rationale to attain synergistic or additive effects, is still higher than ignorable amounts and antagonistic results might seldom be encountered [24]; it was surprising us to find out that combination of our aryl benzofuryl ketoxime moiety with azole residue—both with proven antimycotic activity and gave satisfactory increases in activity introduced alone—in a single molecule did not give the desired successful activity values. Nonetheless, it may be attributed to an unsolicited interaction of the mechanisms involved in these residue's activities or the molecule's changed physicochemical properties with the introduction of the other moiety.

4. Experimental protocols

4.1. Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instrument, FTIR: Schimadzu 8400S spectrophotometer. ^{1}H-NMR: Bruker DPX 400 NMR spectrometer in DMSO-d_6 using TMS as internal standard. MS: VG Platform Mass spectrometer. Analyses for C, H, N was within 0.4% of the theoretical values, Leco CHNS Analyser.

The reaction sequences depicted in Scheme 1 were followed to obtain the new derivatives. Some characteristics of the compounds were given in Table 1.

4.1.1. Aryl (3-methyl-benzofuran-2-yl) ketones (*1*)

The suitable 2′-hydroxyacetophenone (5 mmol), 2-bromoacetophenone (5 mmol) and potassium carbonate (6 mmol) were refluxed in acetonitrile for 4 hours. The solvent was evaporated, the residue was washed with water and crystallised from ethanol.

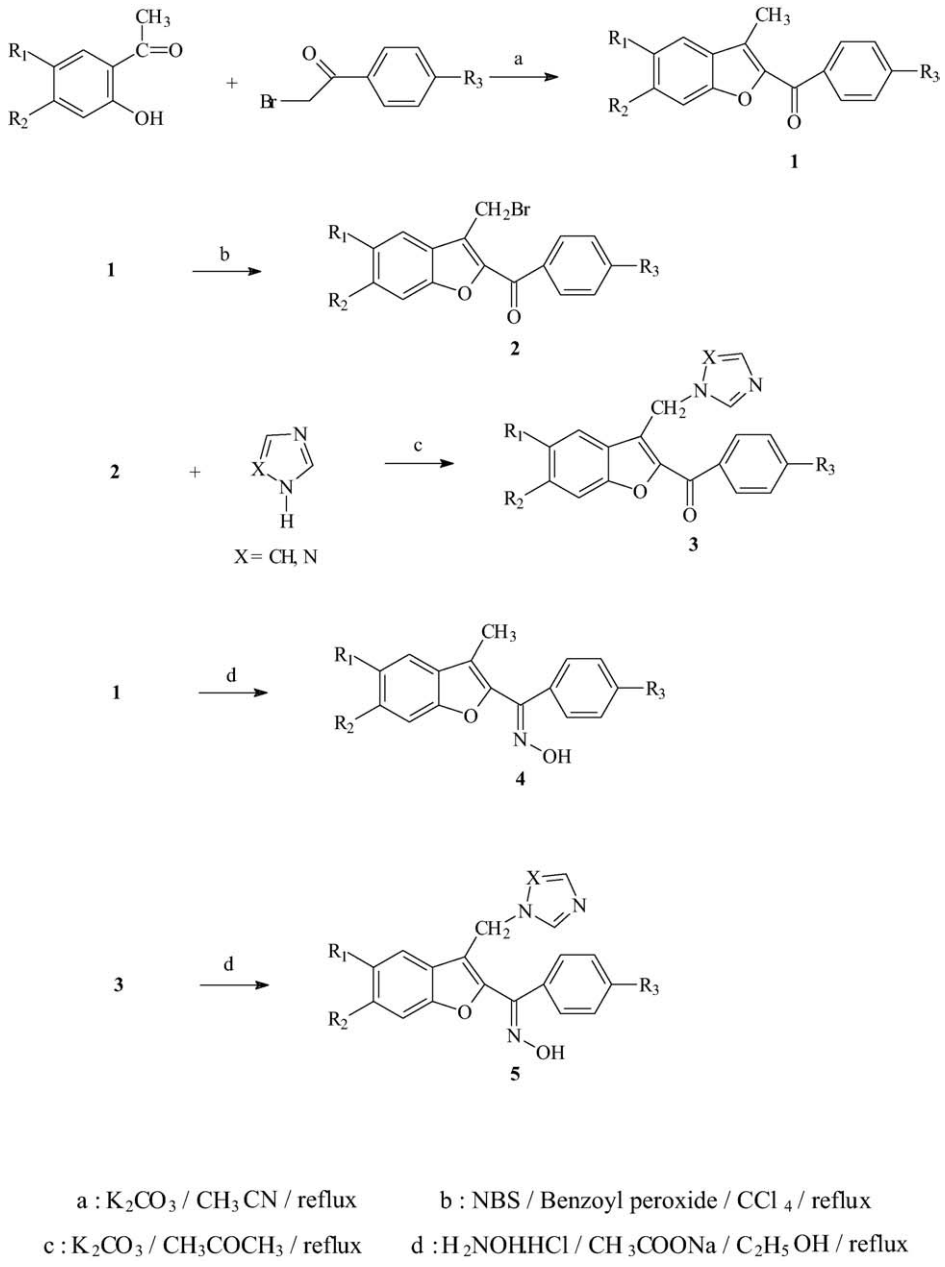
1b IR (KBr) υ_{max} (cm^{-1}): 1645 (C=O), 1647–1564 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.58 (3H, s, CH_3), 7.39–7.43 (1H, m, Ar-H), 7.56–7.60 (1H, m, Ar-H), 7.65–7.69 (3H, m, Ar-H), 7.88 (1H, d, Ar-H), 8.01–8.04 (2H, d, *j*: 8.51 Hz, Ar-H). ES-MS: *m*/*z*: Positive polarity: 271 (M + 1) (100%).

1c IR (KBr) υ_{max} (cm^{-1}): 1643 (C=O), 1640–1552 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.45 (3H, s, CH_3), 2.54 (3H, s, Ar-CH_3), 7.37–7.39 (1H, dd, *j*: 1.41 Hz, *j*: 8.58 Hz, Ar-H), 7.55–7.69 (5H, m, Ar-H), 7.96–7.99 (2H, m, Ar-H).

1f IR (KBr) υ_{max} (cm^{-1}): 1641 (C=O), 1638–1550 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.56 (3H, s, CH_3), 7.59 (1H, dd, *j*: 2.11 Hz, *j*: 8.86 Hz, Ar-H), 7.66–7.68 (2H, d, *j*: 8.54 Hz, Ar-H), 7.74 (1H, d, Ar-H), 8.01–8.03 (3H, m, Ar-H).

4.1.2. Aryl [(3-imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl)] ketones (*3*)

a) The suitable aryl (3-methyl-benzofuran-2-yl) ketone (**1**) (5 mmol), NBS (5 mmol) and benzoyl peroxide (5 mmol) were refluxed in carbontetrachloride for 5 hours. The solvent was evaporated; the residue was washed with water then cold ethanol. No further purification was done and the product was used in the second step.



Scheme 1. Synthesis of the compounds.

b) The suitable aryl [3-(bromomethyl)benzofuran-2-yl] ketone (**2**) (5 mmol), imidazole or 1,2,4-triazole (5.5 mmol) and potassium carbonate (5 mmol) were refluxed in acetone for 2 hours. The solvent was evaporated and the raw product was crystallised from ethanol.

3a IR (KBr) υ_{max} (cm^{-1}): 1647 (C=O), 1638–1553 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.77 (2H, s, $-CH_2-$), 6.47–6.60 (2H, m, Ar-H), 6.86–6.98 (3H, m, Ar-H), 7.06–7.16 (4H, m, Ar-H), 7.89–8.10 (3H, m, imidazole-H). ES-MS: *m*/*z*: Positive polarity: 303 (M + 1) (100%).

3f IR (KBr) υ_{max} (cm^{-1}): 1643 (C=O), 1640–1564 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.92 (2H, s, $-CH_2-$), 7.59–7.63 (3H, m, Ar-H), 7.71–7.75 (2H, m, Ar-H), 7.80–7.82 (1H, d, Ar-H), 7.99 (1H, s, Ar-H), 8.05–8.07 (2H, m, triazole-H and Ar-H), 8.75 (1H, s, triazole-H). ES-MS: *m*/*z*: Positive polarity: 337.9 (M + 1) (75%), 286.2 (100%).

4.1.3. Aryl (3-methyl-benzofuran-2-yl) ketoximes (4)

The suitable aryl (3-methyl-benzofuran-2-yl) ketone (**1**) (5 mmol), hydroxylamine hydrochloride (7 mmol) and anhydrous sodium acetate (7 mmol) were refluxed in ethanol for 3 hours. The reaction mixture was cooled. The crystalline of raw product was filtered and recrystallised from ethanol.

4b IR (KBr) υ_{max} (cm^{-1}): 3254 (O–H), 1629–1521 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.15 and 2.20 (3H, two s, CH_3), 7.27–7.39 (2H, m, Ar-H), 7.42–7.48 (4H, m, Ar-H), 7.52–7.56 (1H, m, Ar-H), 7.64–7.71 (1H, m, Ar-H), 11.95 and 12.26 (1H, two s, OH).

Table 1
Some characteristics of the compounds

Compounds	R_1	R_2	R_3	X	M.p. (°C)	Yield (%)	Molecular formula (Anal. C, H, N)	Molecular weight
1a	H	H	H	–	202	63	$C_{16}H_{12}O_2$	236.27
1b	H	H	Cl	–	105	70	$C_{16}H_{11}ClO_2$	270.72
1c	CH_3	H	H	–	84	64	$C_{17}H_{14}O_2$	250.30
1d	CH_3	H	Cl	–	121	67	$C_{17}H_{13}ClO_2$	284.74
1e	Cl	H	H	–	103	68	$C_{16}H_{11}ClO_2$	270.72
1f	Cl	H	Cl	–	123	65	$C_{16}H_{10}Cl_2O_2$	305.16
1g	H	OCH_3	H	–	85	62	$C_{17}H_{14}O_3$	266.30
1h	H	OCH_3	Cl	–	117	64	$C_{17}H_{13}ClO_3$	300.74
3a	H	H	H	CH	168	64	$C_{19}H_{14}N_2O_2$	302.34
3b	H	H	H	N	160	57	$C_{18}H_{13}N_3O_2$	303.32
3c	H	H	Cl	CH	186	62	$C_{19}H_{13}ClN_2O_2$	336.78
3d	H	H	Cl	N	203	54	$C_{18}H_{12}ClN_3O_2$	337.77
3e	Cl	H	H	CH	94	57	$C_{19}H_{13}ClN_2O_2$	336.78
3f	Cl	H	H	N	163	61	$C_{18}H_{12}ClN_3O_2$	337.77
3g	Cl	H	Cl	CH	280	70	$C_{19}H_{12}Cl_2N_2O_2$	371.23
3h	Cl	H	Cl	N	250	68	$C_{18}H_{11}Cl_2N_3O_2$	372.21
4a	H	H	H	–	113[a]	71	$C_{16}H_{13}NO_2$	251.29
4b	H	H	Cl	–	125[a]	81	$C_{16}H_{12}ClNO_2$	285.73
4c	CH_3	H	H	–	134	65	$C_{17}H_{15}NO_2$	265.31
4d	CH_3	H	Cl	–	144	68	$C_{17}H_{14}ClNO_2$	299.76
4e	Cl	H	H	–	157	72	$C_{16}H_{12}ClNO_2$	285.73
4f	Cl	H	Cl	–	180	76	$C_{16}H_{11}Cl_2NO_2$	320.18
4g	H	OCH_3	H	–	121	64	$C_{17}H_{15}NO_3$	281.31
4h	H	OCH_3	Cl	–	134	68	$C_{17}H_{14}ClNO_3$	315.76
5a	H	H	H	CH	121	45	$C_{19}H_{15}N_3O_2$	317.35
5b	H	H	H	N	124	46	$C_{18}H_{14}N_4O_2$	318.34
5c	H	H	Cl	CH	140	43	$C_{19}H_{14}ClN_3O_2$	351.80
5d	H	H	Cl	N	138	52	$C_{18}H_{13}ClN_4O_2$	352.78
5e	Cl	H	H	CH	179	53	$C_{19}H_{14}ClN_3O_2$	351.80
5f	Cl	H	H	N	262	55	$C_{18}H_{13}ClN_4O_2$	352.78
5g	Cl	H	Cl	CH	247	50	$C_{19}H_{13}Cl_2N_3O_2$	386.24
5h	Cl	H	Cl	N	198	53	$C_{18}H_{12}Cl_2N_4O_2$	387.23

[a] Ref. [16].

4c IR (KBr) υ_{max} (cm^{-1}): 3221 (O–H), 1634–1546 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.12 (3H, s, CH_3), 2.43 (3H, s, Ar-CH_3), 7.11–7.18 (2H, dq, *j*: 1.32 Hz, *j*: 8.4 Hz, Ar-H), 7.23–7.35 (1H, d, Ar-H), 7.38–7.48 (5H, m, Ar-H), 12.61 (1H, s, OH). ES-MS: *m/z*: Positive polarity: 266 (M + 1) (100%), Negative polarity: 264 (M – 1) (100%).

4d IR (KBr) υ_{max} (cm^{-1}): 3272 (O–H), 1616–1568 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.14 and 2.22 (3H, two s, CH_3), 2.40 and 2.43 (3H, two s, Ar-CH_3), 7.13–7.19 (2H, dq, *j*: 1.34 Hz, *j*: 8.45 Hz, Ar-H), 7.34–7.36 (1H, d, Ar-H), 7.40–7.48 (3H, m, Ar-H), 7.51–7.54 (1H, m, Ar-H), 11.94 and 12.26 (1H, two s, OH).

4e IR (KBr) υ_{max} (cm^{-1}): 3123 (O–H), 1621–1552 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.13 and 2.15 (3H, two s, CH_3), 7.32–7.53 (5H, m, Ar-H), 7.58–7.60 (1H, d, Ar-H), 7.74–7.80 (2H, dd, Ar-H), 11.93 and 12.23 (1H, two s, OH).

4f IR (KBr) υ_{max} (cm^{-1}): 3216 (O–H), 1628–1553 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.20 (3H, s, CH_3), 7.32–7.41 (2H, dq, *j*: 1.93 Hz, *j*: 8.72 Hz, Ar-H), 7.44–7.60 (3H, m, Ar-H), 7.74–7.80 (2H, dd, Ar-H), 13.62 (1H, bs, OH).

4h IR (KBr) υ_{max} (cm^{-1}): 3250 (O–H), 1623–1595 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.12 and 2.16 (3H, two s, CH_3), 3.77 and 3.80 (3H, two s, Ar-OCH_3), 6.86–7.08 (2H, dq, *j*: 2.07 Hz, *j*: 8.6 Hz, Ar-H), 7.11–7.17 (2H, dd, Ar-H), 7.42–7.58 (3H, m, Ar-H), 11.80 and 12.18 (1H, two s, OH). ES-MS: *m/z*: Positive polarity: 316 (M + 1) (100%), Negative polarity: 314 (M – 1) (100%).

*4.1.4. Aryl [(3-imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl)] ketoximes (**5**)*

The suitable aryl [(3-imidazol-1-yl/triazol-1-ylmethyl)benzofuran-2-yl)] ketone (**3**) (5 mmol), hydroxylamine hydrochloride (7 mmol) and anhydrous sodium acetate (7 mmol) were refluxed in ethanol for 3 hours. The reaction mixture was cooled. The crystalline of raw product was filtered and recrystallised from ethanol.

Table 2
Antifungal activities of the compounds as MIC (μg ml^{-1})

Compounds	*C. albicans* (NRRL Y-27077)	*C. albicans* (Clinical isolate)	*C. glabrata* (ATCC 36583)
1a	25	25	5
1b	25	25	5
1c	50	50	5
1d	50	50	5
1e	25	50	12.5
1f	25	25	12.5
1g	25	25	12.5
1h	50	50	12.5
3a	25	25	5
3b	25	25	12.5
3c	25	25	12.5
3d	25	25	12.5
3e	25	25	12.5
3f	25	25	5
3g	25	25	12.5
3h	25	25	5
4a	25	25	12.5
4b	5	12.5	5
4c	12.5	12.5	5
4d	5	12.5	5
4e	5	12.5	5
4f	5	12.5	5
4g	12.5	12.5	5
4h	5	12.5	5
5a	12.5	12.5	5
5b	12.5	12.5	5
5c	25	25	5
5d	25	25	12.5
5e	25	25	5
5f	25	25	12.5
5g	12.5	25	12.5
5h	12.5	25	5
Ketoconazole	12.5	12.5	12.5

5a IR (KBr) υ_{max} (cm^{-1}): 3115 (O–H), 1643–1525 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.42 (2H, s, –CH_2–), 6.83–8.09 (12H, m, Ar-H), 12.64 (1H, s, OH).

5c IR (KBr) υ_{max} (cm^{-1}): 3126 (O–H), 1635–1534 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.32 (2H, s, –CH_2–), 7.06–8.39 (11H, m, Ar-H), 12.87 (1H, s, OH). ES-MS: *m*/*z*: Positive polarity: 352 (M + 1) (100%).

5e IR (KBr) υ_{max} (cm^{-1}): 3118 (O–H), 1638–1510 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.28 and 5.42 (2H, two s, –CH_2–), 6.86–7.91 (11H, m, Ar-H), 12.37 and 12.80 (1H, two s, OH). ES-MS: *m*/*z*: Positive polarity: 352 (M + 1) (100%).

5f IR (KBr) υ_{max} (cm^{-1}): 3124 (O–H), 1636–1517 (C=N, C=C). ^{1}H-NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.63 (2H, s, –CH_2–), 7.35–7.47 (5H, m, Ar-H), 7.56–7.58 (1H, d, Ar-H), 7.69–7.70 (1H, d, Ar-H), 7.98 (1H, s, Ar-H), 8.67 (2H, s, triazole-H), 12.51 (1H, s, OH). ES-MS: *m*/*z*: Positive polarity: 353 (M + 1) (42%), 286.2 (100%), Negative polarity: 351 (M − 1) (100%).

4.2. Microbiology

The study was designed to compare MICs obtained by the NCCLS reference M27-A2 broth macrodilution method [25]. Twice MIC readings were performed by each chemical agent. For the antimycotic assays the compounds were dissolved in DMSO. Further dilutions of the compounds and standard drug in test medium were prepared at the required quantities of 100, 75, 50, 25, 12.5, 5, 1, 0.5 μg ml^{-1} concentrations with Sabouraud dextrose broth. In order to ensure that the solvent per se had no effect on yeast growth, a control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in our experiments and found inactive in culture medium. All the compounds were tested for their in vitro growth inhibitory activity against the yeast *C. albicans* (NRRL Y-27077), *C. albicans* (clinical isolate obtained from Faculty of Medicine, Osmangazi University, Eskişehir, Turkey) and *C. glabrata* (ATCC 36583).

Ketoconazole was used as control drug. The observed data on the antifungal activity of the compounds and the control drug are given in Table 2.

4.2.1. Antifungal assay

The cultures were obtained from Sabouraud dextrose broth (Difco) at pH 7 and the twofold serial dilutions technique was applied. The final inoculum size was 5×10^3 CFU ml^{-1} for antifungal assay. A set of tubes containing only inoculated broth was kept as controls. For the antifungal assay after incubation for 24 h at 35 °C, the last tube with no growth of yeast was recorded to represent the MIC expressed in μg ml^{-1}. Every experiment in the antifungal assays was replicated twice in order to define the MIC values.

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