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NEW HETEROCYCLIC OXIME ETHERS OF 1-(BENZOFURAN-2-YL)ETHAN-1-ONE AND THEIR ANTIMICROBIAL ACTIVITY

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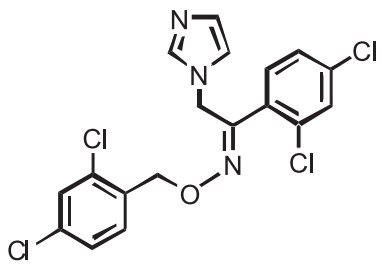
Abstract: In this study, some *O*-benzyl (benzofuran-2-yl)ethan-1-one ether oximes were synthesized starting from 2-acetylbenzofuran. The structure elucidation of the compounds was performed by IR, ^{1}H-NMR and ^{13}C-NMR spectra. Antimicrobial activities of the compounds were examined and notable activity was observed.

Keywords: *O*-benzyl (benzofuran-2-yl)ethan-1-one ether oximes; antimicrobial activity, X-ray analysis

The increase in fungal infections have recently emerged as a growing threat to human health. *Candida* infections are adverse in their appearance (1). The increase in fungal infections and the resistance gained to the currently used drugs in recent years directed the studies on obtaining new antifungal drugs (2). The studies on imidazole and triazole structured antifungal drugs were observed. (3, 4). After discovery of oxiconazole **1**, both azole and ether oximes became of interest. Since then, a number of oximes were synthesized and found to be active against fungi (5-10).



1, oxiconazole

It was proved that the activity of compounds increased when one of the aryl residues was heteroaryl (11). Free oximes and their ethers showed higher activities. When the aryl residue was replaced with benzofuran in a bioisosteric approach, significant antifungal activity was observed (12). In this study, we aimed to obtain compounds derived from oxiconazole, oxime-containing scaffolds. We supposed that if benzofuran is a ring and substituted *O*-benzyl group is in ether oximes, it causes higher activity of such compounds.

Benzofuran is a unique scaffold that is associated with several biological activities. The broad spectrum antifungal (13, 14) and antibacterial activity (15, 16) of these compounds could lead to a new series of antimicrobials. Highly effective compounds were obtained due to aryl benzofuryl ketoximes (17).

EXPERIMENTAL

Chemistry

All reagents were commercially available or synthesized following the procedures described in

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the literature. All NMR spectra were recorded on a Bruker Avance III 700 MHz and Bruker Avance III 400 MHz spectrometer, using $CDCl_3$ as solvent, with TMS as an internal standard. The IR spectra were recorded on Shimadzu FTIR-8400 S spectrometer.

Melting points were determined using an Electrothermal 9100 digital melting point apparatus and were uncorrected.

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone oxime (3)

The suitable 1-(1-benzofuran-2-yl)ethanone (**2**) (3.20 g, 20 mmol), hydroxylamine hydrochloride (1.95 g, 28 mmol) and anhydrous sodium acetate (28 mmol) were refluxed in anhydrous ethanol for 6 h. The reaction mixture was cooled. The crystalline raw product was filtered and recrystallized from anhydrous ethanol (12).

Yield 61%; colorless solid, m.p. 153-154°C, lit. m.p. 155-156°C (18). IR (KBr, cm^{-1}): 3195 (OH). ^{1}H NMR (700 MHz, $CDCl_3$, δ, ppm): 2.37 (s, 3H, CH_3), 2.50 (s, 1H, OH), 7.04 (d, *J* = 0.7 Hz, 1H, CH), 7.28 (dd, *J* = 0.7 Hz, *J* = 7.0 Hz, 1H, CH), 7.37 (ddd, *J* = 0.7 Hz, *J* = 1.4 Hz, *J* = 8.4 Hz, 1H, CH), 7.56 (d, *J* = 8.4 Hz, 1H, CH), 7.62 (dd, *J* = 0.7 Hz, *J* = 8.4 Hz, 1H, CH).

General procedure for preparation of the oxime ethers 4-11 (12)

A mixture of oxime ketone **2** (4 mmol), appropriate benzyl bromide (4 mmol) and potassium carbonate were refluxed in acetone for 8 h. The solvent was evaporated and the residue was washed with water and dried with anhydrous magnesium sulfate. Raw products were crystallized from anhydrous ethanol.

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(4-nitrobenzyl) oxime (4)

Yield 69%, yellow needles, m.p. 127-128°C. IR (KBr, cm^{-1}): 1605 (C=N). ^{1}H NMR (700 MHz, $CDCl_3$, δ, ppm): 2.36 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 7.05 (d, *J* = 0.7 Hz, 1H, CH), 7.27 (dd, *J* = 0.7 Hz, *J* = 7.0 Hz, 1H, CH), 7.36 (dt, *J* = 1.4 Hz, *J* = 7.0 Hz, 1H, CH), 7.55 (d, *J* = 7.0 Hz, 1H, CH), 7.59 (spin system AA', dt, *J* = 1.4 Hz, *J* = 9.1 Hz, 2H, 2×CH), 7.61 (dd, *J* = 7.7 Hz, 1H, CH), 8.26 (spin system BB', dt, *J* = 2.1 Hz, *J* = 9.1 Hz, 2H, 2×CH). ^{13}C NMR (176 MHz, $CDCl_3$, δ, ppm): 12.35 (CH_3), 75.22 (CH_2), 107.37 (CH), 111.73 (CH), 121.45 (CH), 123.28 (CH), 123.69 (2×CH), 125.85 (CH), 127.82 (C), 128.24 (2×CH), 145.21 (C), 147.57 (C), 148.58 (C), 151.35 (C), 155.25 (C).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(4-chlorobenzyl) oxime (5)

Yield 67%, white needles m.p. 108°C. IR (KBr, cm^{-1}): 1615 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.30 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.01 (d, *J* = 0.8 Hz, 1H, CH), 7.25 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H, CH), 7.35 (dt, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H, CH), 7.36-7.40 (m, 4H, 4×CH), 7.56 (dd, *J* = 0.8 Hz, *J* = 8.4 Hz, 1H, CH), 7.60 (dd, *J* = 0.8 Hz, *J* = 8.4 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.92 (CH_3), 75.88 (CH_2), 104.05 (CH), 112.25 (CH), 121.62 (CH), 122.87 (C), 123.89 (CH), 125.88 (CH), 128.20 (C), 130.05 (2×CH), 131.98 (2×CH), 136.84 (C), 147.52 (C), 151.20 (C), 155.19 (C).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(2,4-dichlorobenzyl) oxime (6)

Yield 70%, white needles m.p. 113-114°C. IR (KBr, cm^{-1}): 1612 (C=N). ^{1}H NMR (700 MHz, $CDCl_3$, δ, ppm): 2.36 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 7.05 (d, *J* = 0.7 Hz, 1H, CH), 7.27 (dd, *J* = 0.7 Hz, 1H, CH), 7.30 (dd, *J* = 2.1 Hz, *J* = 7.7 Hz, 1H, CH), 7.36 (dt, *J* = 1.4 Hz, 7.0 Hz, 1H, CH), 7.45 (dd, *J* = 2.1 Hz, *J* = 2.8 Hz, 2H, 2×CH), 7.58 (dt, *J* = 0.7 Hz, *J* = 8.4 Hz, 1H, CH), 7.61 (dt, *J* = 0.7 Hz, *J* = 8.4 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.29 (CH_3), 73.27 (CH_2), 107.13 (CH), 111.74 (CH), 121.40 (CH), 123.22 (CH), 125.73 (CH), 127.08 (CH), 127.88 (C), 129.26 (CH), 130.36 (CH), 133.95 (C), 134.15 (C), 148.36 (C), 151.55 (C), 155.25 (C).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(4-bromobenzyl) oxime (7)

Yield 79%, white solid, m.p. 110-111°C. IR (KBr, cm^{-1}): 1616 (C=N). ^{1}H NMR (700 MHz, $CDCl_3$, δ, ppm): 2.36 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 7.04 (d, *J* = 0.7 Hz, 1H, CH), 7.26 (dd, *J* = 0.7 Hz, *J* = 7.0 Hz, 1H, CH), 7.36 (ddd, *J* = 0.7 Hz, *J* = 1.4 Hz, *J* = 7.0 Hz, 1H, CH), 7.56 (dd, *J* = 0.7 Hz, *J* = 8.4 Hz, 1H, CH), 7.59 (spin system BB`, d, *J* = 9.1 Hz, 2H, 2×CH), 7.61 (d, *J* = 7.7 Hz, 1H, CH), 8.25 (spin system AA', d, *J* = 9.1 Hz, 2H, 2×CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.01 (CH_3), 76.69 (CH_2), 101.69 (CH), 112.44 (CH), 122.08 (CH), 122.67 (C), 123.91 (CH), 126.39 (CH), 128.62 (C), 130.57 (2×CH), 132.28 (2×CH), 137.22 (C), 148.66 (C), 152.39 (C), 155.93 (C).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(4-bromo-2-fluorobenzyl) oxime (8)

Yield 72%, white solid, m.p. 88-89°C. IR (KBr, cm^{-1}): 1604 (C=N). ^{1}H NMR (400 MHz,

$CDCl_3$, δ, ppm): 2.30 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 7.02 (d, *J* = 0.8 Hz, 1H, CH), 7.25 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.30 (dd, *J* = 2.0 Hz, *J* = 4.0 Hz, 1H, CH), 7.33 (d, *J* = 1.6 Hz, 1H, CH), 7.35-7.39 (m, 2H), 7.57 (ddd, *J* = 0.8 Hz, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H, CH), 7.61 (ddd, *J* = 0.8 Hz, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.22 (CH_3), 69.85 (CH_2), 107.01 (CH), 111.73 (CH), 119.21 (CH), 121.38 (CH), 122.22 (C), 123.20 (CH), 124.01 (C), 125.68 (CH), 127.40 (CH), 127.89 (CH), 131.61 (C), 148.23 (CH), 151.55 (C), 155.25 (C), 159.40 (C), 161.91 (C). ^{19}F NMR (376 MHz, CF_3COOH, δ, ppm): -39.31 (dd, *J* = 7.9 Hz, *J* = 8.3 Hz, C-F, 1F).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(4-trifluoromethylbenzyl) oxime (9)

Yield 75%, white solid, m.p. 82-83°C. IR (KBr, cm^{-1}): 1615 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.33 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 7.03 (d, *J* = 1.2 Hz, 1H, CH), 7.26 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H, CH), 7.35 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H, CH), 7.54-7.57 (m, 2H, 2×CH), 7.60 (ddd, *J* = 0.8 Hz, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H, CH), 7.67 (d, *J* = 7.6 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.30 (CH_3), 75.81 (CH_2), 107.11 (CH), 111.73 (CH), 121.39 (CH), 123.22 (CH), 125.33 (CH), 125.37 (C), 125.41 (C), 125.73 (CH), 127.86 (CH), 128.06 (CH), 141.63 (C), 148.20 (C), 148.58 (C), 151.57 (C), 155.24 (C). ^{19}F NMR (376 MHz, CF_3COOH, δ, ppm): 13.48 (s, 3F, CF_3).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(2-fluorobenzyl) oxime (10)

Yield 64%, white-yellow solid, m.p. 58-59°C. IR (KBr. cm^{-1}): 1618 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.31 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 7.02 (d, *J* = 0.8 Hz, 1H, CH), 7.10 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.18 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.25 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.30-7.37 (m, 2H, 2×CH), 7.51 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.55-7.61 (m, 2H, 2×CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.22 (CH_3), 70.50 (CH_2), 106.84 (CH), 111.73 (CH), 115.46 (C), 123.16 (CH), 124.08 (CH), 124.67 (C), 125.60 (CH), 127.95 (CH), 129.82 (CH), 130.56 (CH), 147.95 (C), 151.80 (C), 155.23 (C), 159.72 (C), 162.19 (C). ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): -42.17 (ddd, *J* = 6.8 Hz, *J* = 7.5 Hz, *J* = 8.3 Hz, C-F, 1F).

(*E*)-1-(benzo[*b*]furan-2-yl)ethanone *O*-(2,6-difluorobenzyl) oxime (11)

Yield 69%, white needles, m.p. 73-75°C. IR (KBr, cm^{-1}): 1626 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.25 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 6.95 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 2H, 2×CH), 7.00 (d, *J* = 0.8 Hz, 1H, CH), 7.25 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 1H, CH), 7.31-7.37 (m, 2H, 2×CH), 7.58 (dd, *J* = 0.8 Hz, *J* = 7.2 Hz, 2H, 2×CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.04 (CH_3), 64.11 (CH_2), 106.71 (CH), 111.18 (C), 111.43 (C), 111.73 (CH), 112.92 (C), 121.34 (CH), 123.13 (CH), 125.54 (CH), 127.97 (CH), 130.54 (CH), 148.03 (CH), 151.80 (C), 155.21 (C), 160.99 (C), 163.49 (C). ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): -38.18 (t, *J* = 6.8 Hz, 2F, 2×C-F)

Crystal structure determination of 10

Crystal data: $C_{17}H_{14}FNO_2$, M_r = 283.29, monoclinic, space group $P2_1/n$, *a* = 10.2639(3), *b* = 5.7270(2), *c* = 23.9296(7) Å, β = 94.132(3)§, *V* = 1402.97(7) Å^3, *T* = 293(2) K, *Z* = 4 (*Z*' = 1).

Data collection: A colorless block crystal (ethanol) of 0.40 × 0.22 × 0.13 mm was used to record 16216 (Mo*K*α radiation, θ_{max} = 29.09°) intensities on an Agilent Xcalibur A diffractometer. Intensity data collection employed the ω- scans mode with "Enhance (Mo) X-ray Source". The data were corrected for Lorentz and polarization effects. Data reduction and analysis were carried out with the CrysAlis PRO program (19). The 3506 total unique reflections (R(int) = 0.023) were used for further calculations.

Structure solution and refinement: The structure was solved by the direct methods using the program SHELXS-97 (20) and refinement was done against F^2 for all data using SHELXL-97 (20). The positions of the H atoms were positioned geometrically and were refined using a riding model, with C–H = 0.96 Å (CH_3), 0.97 Å (CH_2), 0.93 Å ($C_{sp}2H$) and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C) for methyl H atoms. The methyl group was refined as a rigid group, which was allowed to rotate. The final refinement converged with *R* = 0.0492 (for 2399 data with $I > 2\sigma(I)$), *wR* = 0.1369 (on F^2 for all data), and *S* = 1.048 (on F^2 for all data). The largest difference peak and hole were 0.294 and -0.218 eÅ^{-3}. The molecular illustration was drawn using ORTEP-3 for Windows (21). Software used to prepare material for publication was WINGX (21) and PLATON (22).

The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ (UK), phone: (+44) 1223/336 408, fax: (+44) 1223/336 033, e-mail: deposit@ccdc.cam.ac.uk, World Wide. Web:http://www.ccdc.cam.ac.uk (deposition No. CCDC 975847).

Antibacterial and antifungal activity

The antimicrobial activities of the compounds were determined using the broth microdilution reference method (23) in standard 96-well polystyrene plates (Kartell). The tested microorganisms were Gram-negative *Escherichia coli* ATTC 25922 and Gram-positive *Staphylococcus aureus* ATCC 25923 bacteria, the yeasts *Candida albicans* and *Malessezia pachydermatis* CBS7925. The study was carried out using microdilution method with the following dilutions of the tested compounds from 400 to 6.25 μg/mL for *Malessezia* (24) and from 512 to 0.125 μg/mL for bacteria and *Candida*.

The bacterial strains were cultivated in Luria-Bertani (LB) broth and the yeast in Sabouraud dextrose broth (SDB). The tested compounds were dissolved in dimethyl sulfoxide (DMSO); diluted tenfold with culture broth to a concentration of 1.024 mg/mL, and then serially diluted in the appropriate medium. The wells were inoculated with the tested strains to a final concentration of 10^4 CFU/mL. The control sample included inoculated growth medium without the compound. In all the tests, DMSO was used as the control; DMSO had no effect on the microorganisms in the concentrations studied (up to 2.5%). Ampicillin (Polfa Tarchomin SA) and itraconazole (Janssen-Cilag International NV) were used as antibiotic reference for the bacteria and yeast, respectively. The plates were incubated at 37°C for 24 h for the bacteria, 48 h for *Candida* and 72 h for *Malessezia*. The microbial growth rate was measured as an optical density at 550 nm (OD_{550}). The tests were performed in triplicate for each concentration.

The minimum inhibitory concentrations (MIC) were defined as the lowest concentration of the compounds at which no visible growth of the tested microorganism occurred.

RESULTS AND DISCUSSION

Chemistry

The final products (**4**-**11**) were synthesized as outlined in Scheme 1. Ketone **2** was prepared from salicylic aldehyde with chloroacetone (25). The (*E*)-oxime **3** was prepared from ketone **2** and recrystallized from ethanol.

Oxime **3** was reacted with appropriate substituted benzyl bromides with high yields. The oxime ethers can be prepared in a reaction with oxime and sodium (26) or sodium hydride (27).

As expected, the presence of *E* and *Z* isomers of the oxime derivatives was observed in the raw products. All the final products were crystallizes from ethanol. Thus, no isomers *Z* were observed in the final products; in the NMR spectra aliphatic pro-

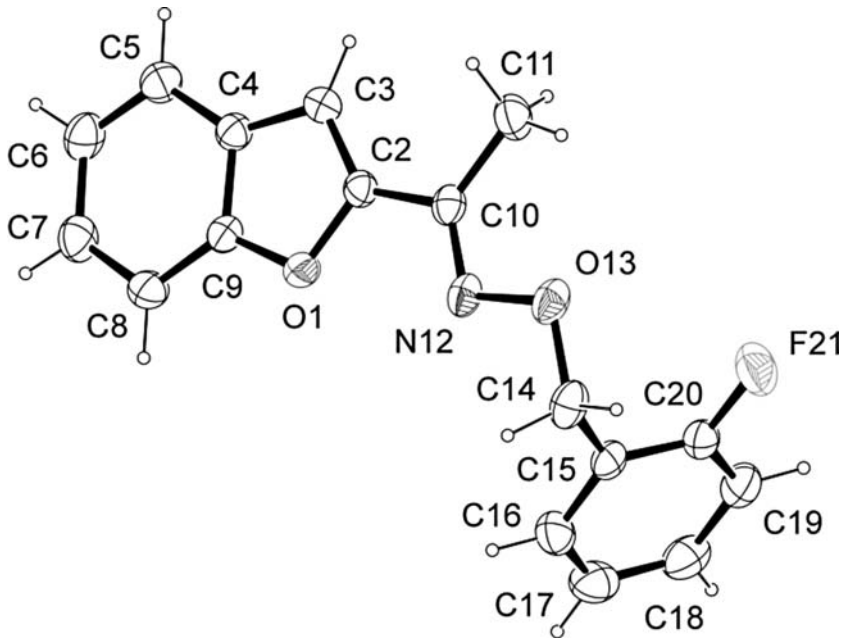
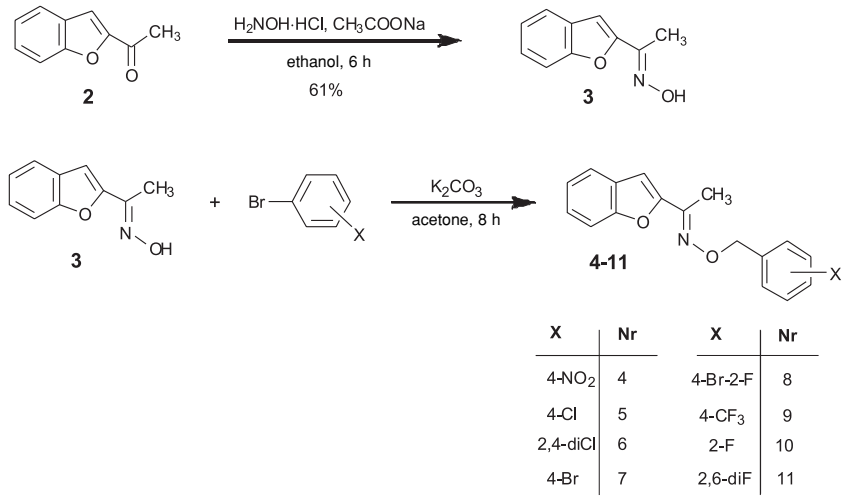


Figure 1. The molecular structure of compound **10** showing the atom labelling scheme. Non-H atoms are drawn as 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radius



X	Nr	X	Nr
4-NO_2	4	4-Br-2-F	8
4-Cl	5	4-CF_3	9
2,4-diCl	6	2-F	10
4-Br	7	2,6-diF	11

Scheme 1. Reaction sequence for the synthesis of ether oximes **4**-**11**

Table 1. Antibacterial and antifungal activities of the compounds **4**-**11** and the standard drugs used in the study (MIC μg/mL).

Compound	MIC [μg/mL]		
	Staphylococcus aureus	*Escherichia coli*	*Candida albicans*
4	> 512	512	512
5	> 512	512	512
6	256	> 512	512
7	256	512	512
8	256	256	512
9	128	512	512
10	256	512	256
11	256	512	256
Itraconazole	-	-	2
Ampicillin	8	8	-

tons were not resonated in two different groups with corresponding integral values. We have prepared a few fluorinated products **8**-**11**, supposedly being highly effective. Structural features of synthesized heterocyclic oxime ethers of 1-(benzofuran-2-yl)ethan-1-one were confirmed by X-ray crystallographic analysis of exemplified compound **10**.

Crystallographic data

The molecular structure of compound **10** and the atom-labelling scheme is illustrated in Figure 1.

The nine-membered benzofuran system is planar with an r.m.s. deviation of 0.0083 Å and is in *E* configuration with respect to the 2-fluorobenzyloxy moiety [torsion angle C2-C10-N12-O13: -178.87 (11)°]. Simultaneously, conjugated system of double bonds C2 = C3 and C10 = N12 has *s-trans* conformation [torsion angle C3-C2-C10-N12: 179.62 (16)°].

The interatomic distance C10 = N12 takes the value of 1.286(2) Å and confirms the occurrence of the double bond between these atoms.

Angular orientation of the 2-fluorobenzyloxy fragment in the molecule reveal three torsional angles C10-N12-O13-C14, N12-O13-C14-C15 and O13-C14-C15-C16 of -174.93(13), 74.23(16) and

66.49(19)°, respectively. The first one indicates that the C10-N12 and O13-C14 bonds are antiperiplanar to each other while the second and the third torsional angles both reveal mutual synclinal orientation of the bonds N12-O13 and C14-C15 or O13-C14 and C15-C16. The phenyl ring of the 2-fluorobenzyloxy moiety forms a dihedral angle of 80.03(5)° with the planar benzofuran system.

Antimicrobial activity

The antimicrobial activity of the synthesized compounds (**4**-**11**) was evaluated *in vitro* against *E. coli* ATCC 25922, *S. aureus* ATCC 25923, *C. albicans,* and *M. pachydermatis*. The results of the evaluation of their minimal inhibitory concentration values are presented in Table 1. Two standard drugs ampicillin and itraconazole were used as controls; the MIC values obtained for these compounds are 8 and 2 μg/mL, respectively.

The growth of Gram-positive reference strain *S. aureus* was inhibited by compounds **6**, **7**, **8**, **10** and **11** at the concentration of 250 μg/mL. A twofold lower dose (128 μg/mL) was required in the case of derivative **9,** carrying a 4-trifluoromethylbenzyl substituent, to inhibit the growth of *S. aureus*. Of all the tested substances, only compound **8** (4-bromo-2-fluorobenzyl group) was active against *E. coli* (MIC 256 μg/mL). Derivatives **10** and **11**, with 2-fluorine and 2,6-difluorine groups, showed moderate activity against *C. albicans*, MIC values of 250 mg/mL, but were less active than the standard antifungal drug, itraconazole.

The other derivatives examined, i.e., oxime ethers **4** and **5**, were inactive against all the tested microorganisms (MIC ≥ 512 μg/mL).

Evaluation of the antifungal activity of the tested oxime ethers against *M. pachydermatis* showed a slight inhibitory effect at the concentration of 400 μg/mL. The growth of the tested *Malessezia* strains was half less intense as against the positive control - an inoculum of the fungus in Sabouraud medium without the compounds. All the tested derivatives were ineffective at lower concentrations (200-6.25 μg/mL).

Alper-Hayta et al. (16) showed that 2-(substituted phenyl/benzyl)-5-[(2-benzofuryl)carboxamido]-benzoxazole derivatives possessed a broad spectrum of activity against Gram-positive and Gram-negative bacteria as well as *Candida* (MIC range between 15.625-500 μg/mL). Similar results were obtained by other authors; the compounds of cyclobutane substituted benzofuran class were able to inhibit the growth of *C. albicans* and *S. aureus* at the concentration from 2.5 to 0.039 mg/mL (15). The dinaphtho[2,1-*b*]furan-2-yl-methanone compounds and their oxime derivatives showed weak antimicrobial activity against bacteria and *Candida* (128-512 μg/mL) (28).

We have described the synthesis and antibacterial and antifungal activity of new benzofuran-containing oximes. The results obtained showed that these compounds exhibited relatively weak antimicrobial potency against the tested microorganisms. The most promising activity was detected in derivatives **8**–**11** containing fluorine residues.

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Conflicts of interests

The Authors have declared that there is no conflict of interests.

REFERENCES

1. Odds F., Brown A.J.P, Gow N.A.R.: Trends Microbiol. 11, 272 (2003).
2. Benedetti M.S., Bani M.: Drug Metab. Rev. 31, 665 (1999).
3. Wolf M.E.: Burger`s Medicinal Chemistry and Drugs Discovery, 5th edn., pp. 1-5, John Wiley & Sons, New York 1997.
4. Lednicer D.: Strategies for Organic Drug Synthesis and Design, 7th edn., pp. 94 and 273, John Wiley & Sons, Hoboken NJ 2009.
5. Mixich G., Thiele K.: US Patent 4,550,175 (1985).
6. Massolini G., Carmellino M.L., Kitsos M., Baruffini A.: Farmaco 48, 503 (1993).
7. Karakurt A., Dalkara S., Özalp M., Özey S., Kendi E. Stables J.P: Eur. J. Med. Chem. 36, 421 (2001).
8. Emami S., Falahati M., Banifetami A., Shafiee A.: Bioorg. Med. Chem. 12, 5881 (2004).
9. De Luca L.:, Curr. Med. Chem. 21, 69 (2006).
10. Attia M.I., Zakaria A.S., Almutairi M.S., Ghoneim S.W.: Molecules 18, 12208 (2013).
11. Massolini G., Carmellino M.L., Baruffini A.:, Farmaco 51, 287 (1996).
12. Demirayak S., Uçucu Ü., Benkli K., Gündoğdu-Karaburun N., Karaburun A., Akar D., Karabacak M., Kiraz N.: Farmaco 57, 609 (2002).
13. Masobuchi M., Ebiike H., Kawasaki K., Sogabe S., Morikami K.: Bioorg. Med. Chem. 11, 4463 (2003).

14. Aslam S.N., Stevenson P.C., Phythian S.J., Veitch N.C., Hall D.R.: Tetrahedron 62, 4214 (2006).
15. Koca M., Servi S., Kilirmis C., Ahmdzade M., Kazaz C.: Eur. J. Med. Chem. 40, 1351 (2005).
16. Alper-Hayta S., Arisoy M., Temiz-Arpaci O., Yildiz I., Aki E.: Eur. J. Med. Chem. 43, 2568 (2008).
17. Gündoğdu-Karaburun N., Benkli K., Tunali Y., Uçucu Ü., Demirayak S.: Eur. J. Med. Chem. 41, 651 (2006).
18. Vargha L., Ramonczari J., Bathory J.: J. Am. Chem. Soc. 71, 2652 (1949).
19. Agilent (2011). CrysAlis PRO. Oxford Diffraction Ltd., Yarnton, England.
20. Sheldrick G.M.: A short history of SHELX, Acta Cryst. A64, 112 (2011).
21. Farrugia L.J.: WinGX and ORTEP for Windows: an update, J. Appl. Cryst. 45, 849 (2012).
22. Spek A.L.: Acta Cryst. D65, 148 (2009).
23. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth dilution. Clin. Microbiol. Infect., 9, ix (2003).
24. Michael A., Pfaller M.D.: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard, Sec. Edit. CLSI Document M27-A2 (2002), Wayne, Pennsylvania, USA.
25. Elliot E.D.: J. Am. Chem. Soc. 73, 754 (1951).
26. Karakurt A., Dalkaraa S., Özalp M., Özbey S., Kendi E., Stables J.P.: Eur. J. Med. Chem. 36, 421 (2001).
27. Bosiak M., Krzemiński M.P., Jaisankar P., Zaidlewicz M.: Tetrahedron Asymmetry, 19, 956 (2008).
28. Kilirmiş C., Koca M., Servi S., Gür S.: Turk. J. Chem. 33, 375 (2009)

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