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Synthesis and Antifungal Activity of New Nitrobenzofuran Derivatives

Ahmet Çağrı KARABURUN[1*]

ABSTRACT: The object of present study is to assess anticandidal activities of some new aryl (5-nitrobenzofuran-2-yl)keton and ketoxime compounds. Eight aryl (5-nitrobenzofuran-2-yl)ketones and ketoximes were synthesized. IR, ^{1}H-NMR and HR-MS spectroscopic data, performed the structure elucidation of the synthesized compounds. Anticandidal activities of the all synthesized compounds were studied. Compound **2c** bearing methoxy group on phenyl ring showed the highest activity with MIC value of 3.12 μg mL^{-1} against *Candida albicans* and *Candida glabrata*. None of the compounds activity results were equal to or better than that of the control compounds ketoconazole and fluconazole. However, compound **2c** displayed a promising anticandidal activity.

Keywords: Aryl (5-nitrobenzofuran-2-yl)ketones, aryl (5-nitrobenzofuran-2-yl)ketoximes, anticandidal activity.

Yeni Nitrobenzofuran Türevlerinin Sentezi ve Antifungal Etkileri

ÖZET: Bu çalışmada bazı yeni aril (5-nitrobenzofuran-2-il)keton ve ketoksim bileşiklerinin antikandidal etkinliklerinin değerlendirilmesi amaçlanmıştır. Sekiz aril (5-nitrobenzofuran-2-il)keton ve ketoksimi sentezlenmiştir. Sentezlenen bileşiklerin yapı aydınlatmaları IR, ^{1}H-NMR ve HR-MS spektroskopik verileri ile gerçekleştirilmiştir. Bileşiklerin antikandidal etkinlikleri incelenmiştir. Fenil halkası üzerinde metoksi grubu taşıyan bileşik **2c**, 3.12 μg mL^{-1} MİK değeri ile *Candida albicans* ve *Candida glabrata*'ya karşı en yüksek aktiviteyi göstermiştir. Hiçbir bileşik kontrol bileşikleri olan ketokonazol ve flukonazole eş ya da daha iyi aktivite sergileyememiştir. Ancak, bileşik **2c**'nin aktivite sonuçları umut verici olarak değerlendirilmektedir.

Anahtar Kelimeler: Aril (5-nitrobenzofuran-2-il)ketonlar, aril (5-nitrobenzofuran-2-il)ketoksimler, antikandidal aktivite.

[1] Ahmet Çağrı KARABURUN (**Orcid ID:** 0000-0002-2503-3824), Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Eskişehir, Türkiye

Sorumlu yazar/Corresponding Author: Ahmet Çağrı KARABURUN, e-mail: ackarabu@anadolu.edu.tr

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INTRODUCTION

Worldwide, the physicians draw attention on fungal infections due to the frequency of suffered patients from fungal diseases (Valerio et al., 2015; Benedict et al., 2017). It has been reported by clinical data that the incidence of fungal infections are increased in patients with cancer and tuberculosis since immunity falls or disappears (Sipsas and Kontoyiannis, 2012; Osman et al., 2013). Also, the development of multi-drug and pandrug resistances cause insufficient treatment, especially for one of the largest group of fungal pathogens, *Candida* species which are also the most reported species regarding resistance development (Dos Santos Abrantes et al., 2014; Dimopoulos et al., 2015; Healey et al., 2016). Thus, researchers have focused on the development of more effective agents against opportunistic fungi and they tried to inhibit the development of resistance. On the other hand, it is petitive that these antimicrobial agents to be developed have broad spectrum with low cytotoxicity against human cells (Miyazaki et al., 2011; Ravu et al., 2013).

In medicinal chemistry, benzofuran ring system has a special importance because of its pharmacological properties such as analgesic (Rádl et al., 2000), antinociceptive (Goncalves et al., 2012), antibacterial (Jiang et al., 2011), antifungal (Demirayak et al., 2016), antiviral (Engler et al., 1996), antihypertensive (de Souza Nunes et al., 2014) and anticancer (Mao et al., 2016) activities. Its antifungal activity is supported by recent studies (Telvekar et al., 2012; Geronikaki et al., 2013), which reported the clinical uses of griseofulvin (Grover et al., 2012), in which benzofuran is located as a core structure. Furthermore, griseofulvin has been indicated successful on patients in comparison with other antifungal agents independent of the fungus type (Wallace, 1977; Shemer et al., 2013).

Oximes are used as a constitutive structure to gain biologically active compounds and they are a preference for bioisosteric replacement and protection of carbonyl groups (Primožič et al., 2014). Moreover, having the easy modification for substitutions on oxygen atom, it could increase or maintain the antifungal activity vis-à-vis carbonyl group (Kirilmis et al., 2008).

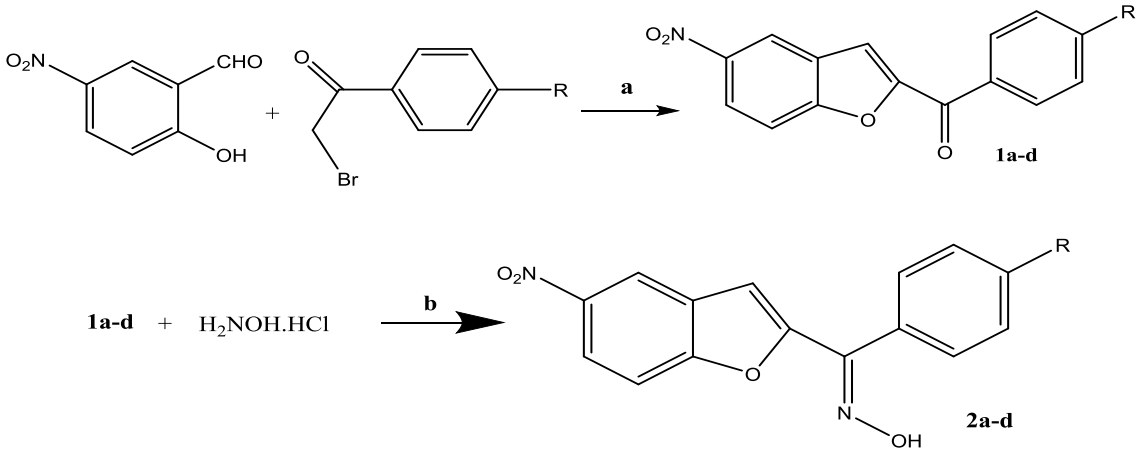
Thus, for the above mentioned reasons eight compounds (**1a**-**1d**, **2a**-**2d**), involved 5-nitrobenzofuran as core structure, were synthesized and analyzed for antifungal activity.

MATERIALS AND METHODS

Chemistry

All chemicals used in the syntheses were purchased either from Sigma-Aldrich Chemicals (Sigma-Aldrich Corp., St. Louis, MO, USA) or Merck Chemicals (Merck KGaA, Darmstadt, Germany). Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were presented as uncorrected. ^{1}H-NMR spectra was recorded by a Bruker 300 MHz digital FT-NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d_6. In the NMR spectra, splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; m: multiplet. Coupling constants (*J*) were reported as Hertz. The IR spectra of the compounds were recorded using an IRAffinity-1S Fourier transform IR (FTIR) spectrometer (Shimadzu, Kyoto, Japan). Mass spectra were recorded on an LCMS-IT-TOF (Shimadzu, Kyoto, Japan) by using ESI method. The purities of compounds were checked by TLC on silica gel 60 F254 (Merck KGaA, Darmstadt, Germany). Aryl (5-nitrobenzofuran-2-yl)ketone derivatives were synthesized in accordance with previous methods (Pestellini et al., 1988).

New compounds were obtained with the reactions depicted in Scheme 1.



R: H, CH_3, OCH_3, Cl a: K_2CO_3 / CH_3CN / reflux b: CH_3COONa / C_2H_5OH / reflux

Scheme 1. Synthetic procedure for the compounds

Some characteristics of the synthesized compounds were given in **Table 1**.

Table 1. Some characteristics of the synthesized compounds

Compounds	R	m.p. (°C)	Yield (%)	Formulae	Mol. Weight
1a	H	205-6*	78	$C_{15}H_9NO_4$	267.24
1b	CH_3	214-5	82	$C_{16}H_{11}NO_4$	281.27
1c	OCH_3	233-4	75	$C_{16}H_{11}NO_5$	297.27
1d	Cl	209-10	87	$C_{15}H_8ClNO_4$	301.69
2a	H	126-7	75	$C_{15}H_{10}N_2O_4$	282.26
2b	CH_3	240-1	80	$C_{16}H_{12}N_2O_4$	296.29
2c	OCH_3	263-4	72	$C_{16}H_{12}N_2O_5$	312.28
2d	Cl	234-5	82	$C_{15}H_9ClN_2O_4$	316.70

* Lit (Vinh et al., 1999) m.p. 203 °C.

Synthesis of Aryl (5-nitrobenzofuran-2-yl)ketones (1a-d)

Aryl (5-nitrobenzofuran-2-yl)ketone derivatives were synthesized in accordance with previous methods (Pestellini et al., 1988).

***(5-Nitrobenzofuran-2-yl)(phenyl)methanone* (1a)**

Yield: 78 %, M.P. = 205-6 ℃, FTIR (ATR, cm^{-1}): 3096, 1645 (C=O), 1090, 800, 696. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 7.63- 7.68 (2H, m, phenyl CH), 7.75- 7.77 (1H, m, phenyl CH), 7.96 (1H, s, BF-H), 7.98 (1H, d, J=9.36 Hz, BF-H), 8.11- 8.14 (2H, m, phenyl CH), 8.48 (1H, dd, J=9.12 Hz-2.43 Hz, BF-H), 8.85 (1H, d, J= 2.37 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_9NO_4$: 268.0604; found 268.0614.

***(5-Nitrobenzofuran-2-yl)(p-tolyl)methanone* (1b)**

Yield: 82 %, M.P. = 214-5 ℃, FTIR (ATR, cm^{-1}): 2986, 1645 (C=O), 1051, 833, 746. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 2.49 (3H, s, CH_3), 7.47 (2H, d, J= 8.19 Hz, methylphenyl CH), 7.93 (1H, s, BF-H), 7.97 (1H, d, J= 9.15 Hz, BF-H), 8.05 (2H, d, J=8.19 Hz,

methylphenyl CH), 8.48 (1H, dd, J=9.15 Hz-2.40 Hz BF-H), 8.84 (1H, d, J= 2.37 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{16}H_{11}NO_4$: 282.0761; found 282.0770.

***(4-Methoxyphenyl)(5-nitrobenzofuran-2-yl)methanone* (1c)**

Yield: 75 %, M.P. = 233-4 ℃, FTIR (ATR, cm^{-1}): 2936, 1639 (C=O), 1063, 800, 752. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 3.97 (3H, s, OCH_3), 7.17 (2H, d, J= 8.94 Hz, methoxyphenyl CH), 7.92 (1H, s, BF-H), 7.97 (1H, d, J= 9.09 Hz, BF-H), 8.18 (2H, d, J=8.94 Hz, methoxyphenyl CH), 8.47 (1H, dd, J=9.15 Hz-2.40 Hz, BF-H), 8.85 (1H, d, J= 2.34 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{16}H_{11}NO_5$: 298.0710; found 298.0723.

***(4-Chlorophenyl)(5-nitrobenzofuran-2-yl)methanone* (1d)**

Yield: 87 %, M.P. = 209-10 ℃, FTIR (ATR, cm^{-1}): 3093, 1661 (C=O), 1092, 800, 748. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 7.70 (2H, d, J= 8.55 Hz, chlorophenyl CH), 7.97-8.00 (2H, m, BF-H), 8.17 (2H, d, J=8.55 Hz, chlorophenyl CH), 8.49 (1H, dd, J=9.00 Hz-2.22 Hz, BF-H), 8.85 (1H, d, J= 2.40 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_8NO_4Cl$: 302.0215; found 302.0225.

Synthesis of Aryl (5-nitrobenzofuran-2-yl)ketoximes (2a-d)

The suitable aryl (5-nitrobenzofuran-2-yl) ketone derivative (5 mmol), **1a-d**, was heated in ethanol with hydroxylamine hydrochloride (7 mmol) for 3 hours with catalyze of anhydrous sodium acetate (7 mmol). After completion of reaction, the mixture was allowed to cool for crystallization. The precipitated product was filtered and recrystallized from ethanol.

***(E/Z)-(5-nitrobenzofuran-2-yl)(phenyl)methanone oxime* (2a)**

Yield: 75 %, M.P. = 126-7 ℃, FTIR (ATR, cm^{-1}): 3379 (O-H), 2988, 1634 (C=O), 1013, 820, 696. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 7.47- 7.65 (5H, m, phenyl CH), 7.75 (1H, d, J=9.32 Hz, BF-H), 8.08 (1H, s, BF-H), 8.33 (1H, dd, J=9.12 Hz-2.40 Hz, BF-H), 8.77 (1H, d, J= 2.37 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{10}N_2O_4$: 283.0713; found 283.0719.

***(E/Z)-(5-nitrobenzofuran-2-yl)(p-tolyl)methanone oxime* (2b)**

Yield: 80 %, M.P. = 240-1 ℃, FTIR (ATR, cm^{-1}): 3202 (O-H), 3001, 1622 (C=O), 1013, 818, 685. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 2.40 (3H, s, CH_3), 7.29 (2H, d, J= 8.01 Hz, methylphenyl CH), 7.52 (2H, d, J=8.13 Hz, methylphenyl CH), 7.77 (1H, d, J= 8.79 Hz, BF-H), 8.05 (1H, s, BF-H), 8.32 (1H, dd, J=8.79 Hz-2.40 Hz, BF-H), 8.76 (1H, d, J= 2.37 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{16}H_{12}N_2O_4$: 297.0870; found 297.0877.

***(E/Z)-(4-methoxyphenyl)(5-nitrobenzofuran-2-yl)methanone oxime* (2c)**

Yield: 72 %, M.P. = 263-4 ℃, FTIR (ATR, cm^{-1}): 3227 (O-H), 2997, 1639 (C=O), 1018, 810, 750. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 3.88 (3H, s, OCH_3), 7.03 (2H, d, J=8.94 Hz, methoxyphenyl CH), 7.58 (2H, d, J=8.94 Hz, methoxyphenyl CH), 7.78 (1H, d, J=9.09 Hz, BF-H), 8.03 (1H, s, BF-H), 8.33 (1H, dd, J=9.09 Hz-2.40 Hz, BF-H), 8.77 (1H, d, J= 2.34 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{16}H_{12}N_2O_5$: 313.0819; found 313.0830.

***(E/Z)-(4-chlorophenyl)(5-nitrobenzofuran-2-yl)methanone oxime* (2d)**

Yield: 82 %, M.P. = 234-5 ℃, FTIR (ATR, cm^{-1}): 3177 (O-H), 3001, 1651 (C=O), 1022, 818, 685. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 7.53 (2H, d, J=8.61 Hz, chlorophenyl CH), 7.69 (2H, d, J=8.61 Hz, chlorophenyl CH), 7.79 (1H, d, J=9.06 Hz, BF-H), 8.11 (1H, s, BF-H), 8.33 (1H, dd, J=9.09 Hz-2.40 Hz, BF-H), 8.78 (1H, d, J= 2.37 Hz, BF-H). HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_9N_2O_4Cl$: 317.0324; found 317.0333.

Antifungal Activity

Anticandidal activity, according to the protocol of the EUCAST (Rodriguez-Tudela et al., 2008), was performed for gained final compounds **1a-d, 2a-d** against *Candida albicans* (ATCC 24433), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019) and *Candida glabrata* (ATCC 90030). Synthesized compounds as well as ketoconazole and fluconazole as reference drugs were tested. The minimum inhibitory concentrations (MICs) of the all synthesized compounds were determined by fluorometric measurements (Palomino et al., 2002; Borra et al., 2009). **Table 2** presents MIC values of all compounds as antifungal results.

Table 2. MIC_{50} (μg mL^{-1}) values of compounds (**1a-d, 2a-d**)

Compounds	*Candida albicans*	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*
1a	50	50	100	100
1b	25	25	50	25
1c	12.50	25	50	50
1d	12.50	50	100	100
2a	25	50	25	100
2b	12.50	12.50	25	50
2c	3.12	3.12	6.25	12.50
2d	6.25	12.50	25	12.50
Ketoconazole	0.78	1.56	1.56	1.56
Fluconazole	0.78	1.56	1.56	0.78

RESULTS AND DISCUSSION

Chemistry

The reactions, depicted in scheme were followed for the synthesis of aryl (5-nitrobenzofuran-2-yl)ketoxime compounds. A slightly altered Rap-Störmer Reaction gave the ketonic compounds, **1a-d**, (Pestellini et al., 1988). The ketones were allowed to react with hydroxylamine hydrochloride to obtain the oxime derivatives (**2a-d**). In evaluation of the spectral data of the synthesized compounds, all data were obtained as expected. In IR spectra; ketone compounds showed characteristic carbonyl stretching bands at about 1640-1660 cm^{-1} region, also oxime compounds showed characteristic O-H bands at about 3200-3400 cm^{-1} region. Characteristic nitro group symmetric and asymmetric stretching bands were observed for all compounds. In ^{1}H-NMR spectra; all aliphatic and aromatic protons were observed as expected with corresponding integral values. However, oxime hydrogens which were effortlessly identified in IR spectra, could not be observed in NMR. It may be attributed to the proton exchange with deutero solvent used in NMR. It is also of consideration that the electron withdrawing effect of nitro group increases the acidity of the oxime which facilitates the proton exchange of this group. For all compounds HRMS spectra showed exact molecular mass and formula.

Antifungal Activity

According to antifungal activity results, all compounds displayed anticandidal activity. Compounds with oxime moiety (**2a-2d**) were found more active than their carbonyl substitution derivatives (**1a-1d**) against *Candida* species. In fact, compound **2c** was found to be the most potent derivative in the series against all *Candida* species with MIC_{50} values of 3.12 and 12.50 μg mL^{-1}. Moreover, it can be seen that

compound **2d** showed remarkable activity against *Candida albicans* with a MIC_{50} value of 6.25 μg mL^{-1}. Also, any substitution at the 4th position of the benzene ring increased anticandidal activity, particularly 4-methoxy substitution was found two times more active than other substitutions. On the other hand, none of the synthesized compounds showed higher activity than the standard drug.

In consideration of the antifungal activity results, it is seen that ketone compounds showed very little activity on tested fungi. When the carbonyl group converted to its oxime, the activity elevated for all compounds. In addition, effect of the substituent positioned on the phenyl ring is crucial for activity. Especially compound **2c** displayed a promising anticandidal activity. Methoxy substitution on the phenyl ring resulted in the highest activity among the synthesized compounds.

CONCLUSION

None of the compounds activity results was equal to or better than that of the control compounds ketoconazole and fluconazole. However, compound **2c** displayed a promising anticandidal activity. In general, it is expected that oxime derivatives of nitrobenzofuran might be promising antifungal candidates. Hence, with further study and synthesis of new oxime derivatives, better nitrobenzofuran antifungal agents can possibly be obtained. This in turn can contribute to the inhibition of the ongoing fungal resistance development to currently available antifungal agents.

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