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Synthesis and antifungal activities of some aryl(benzofuran-2-yl)ketoximes

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Abstract

In this study, some aryl(benzofuran-2-yl)ketoximes and their ethers and esters were synthesised. The structure elucidation of the compounds was performed by IR, ^{1}H NMR and mass spectroscopic data and elemental analyses results. Antifungal activities of the compounds were examined and notable activity was obtained.

Keywords: Aryl(benzofuran-2-yl)ketoximes; Antifungal activity

1. Introduction

The increase in fungal infections in recent years, directed the studies on imidazole and triazole structured antifungal drugs [1,2]. After it was discovered that oxiconazole, i.e. carrying both azole and oxime residue, is a very effective antifungal agent, oximes became of interest. During our literature researches we had observed that benzophenone oximes were effective against phytopathogenic fungi both in vitro and in vivo [1]. It was proved that the activity increased when one of the aryl residues was heteroaryl [3–5] (i.e. pyridine or furane). Besides, it was reported that free oximes and their ethers or esters showed notably higher activities [4]. In consideration of all these findings, in this study, we aimed to obtain aryl(benzofuran-2-yl)ketoximes and their ethers and esters and test their antifungal activity.

2. Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments, IR: Schimadzu 435 IR spectrophotometer, ^{1}H NMR: Bruker DPX 400 NMR spectrometer in DMSO-d_6 using TMS as internal standard. Analyses for C, H, N were within 0.4% of the theoretical values. Aryl(benzofuran-2-yl)ketones were prepared according to the literature method [6].

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

2.1. Aryl(benzofuran-2-yl)ketoximes (2)

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

2a IR (KBr) ν_{max} (cm^{-1}): 3192 (O–H), 1639–1512 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6) δ (ppm): 7.16–7.75 (10H, m, Ar–H), 12.30 (1H, s, O–H).

2c IR (KBr) ν_{max} (cm^{-1}): 3202 (O–H), 1642–1510 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.80 (3H, s, Ar–OCH_3), 6.78 (2H, d, j:8.82 Hz, Ar–H), 7.20–7.74 (7H, m, Ar–H), 12.32 (1H, s, O–H).

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2.2. Aryl(benzofuran-2-yl)-O-alkylketoximes (3)

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

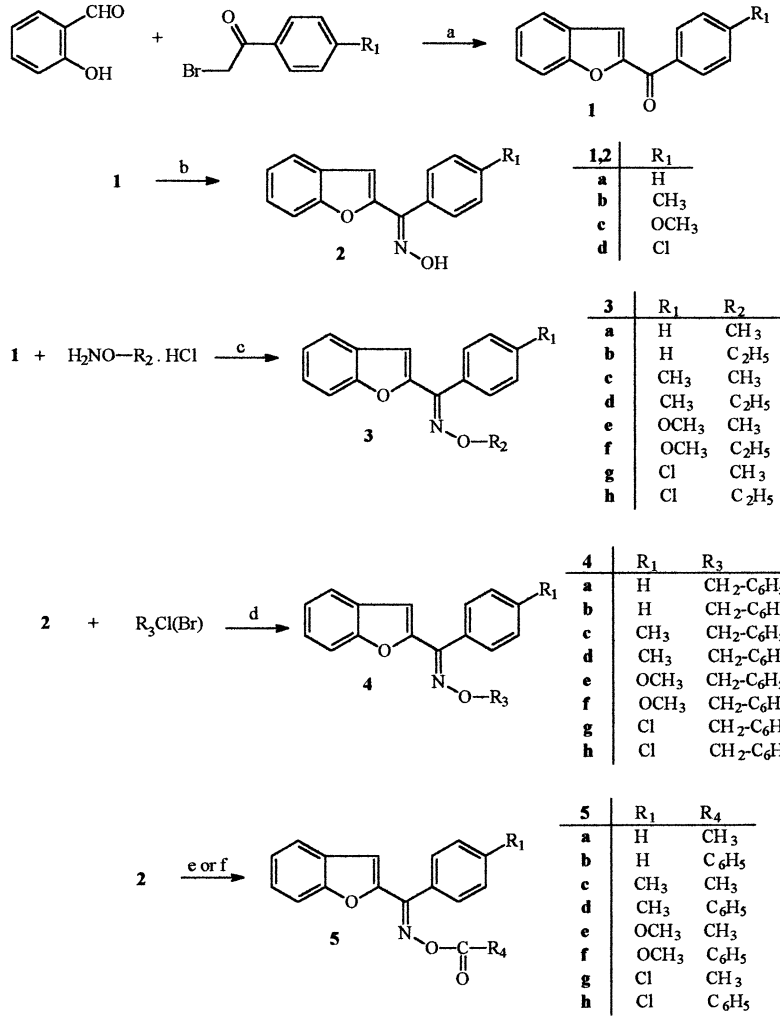
3a IR (KBr) ν_{max} (cm^{-1}): 1642–1510 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.95 and 4.07 (3H, two s, N–O–CH_3), 6.96–7.65 (10H, m, Ar–H), EI MS: m/z: 251.10 [M^+], 236.60, 76.10 (100%).

3e IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.79 and 3.80 (3H, two s, Ar–OCH_3), 4.00 and 4.10 (3H, two s, N–O–CH_3), 6.56 (1H, s, Ar–H), 6.93 (2H, d, j: 8.71 Hz, Ar–H), 7.13–7.49 (2H, m, Ar–H), 7.38 (2H, d, j: 8.65 Hz, Ar–H), 7.43–7.61 (2H, m, Ar–H).

3f IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 1.12 and 1.26 (3H, two t, N–O–CH_2–CH_3), 3.81(3H, s, Ar–OCH_3), 4.09 and 4.18 (2H, two q, N–O–CH_2–CH_3), 6.41 (1H, s, Ar–H), 6.90–7.61 (8H, m, Ar–H).

3g IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.84 and 3.96 (3H, two s, N–O–CH_3), 6.36 (1H, s, Ar–H), 7.01–7.50 (8H, m, Ar–H), EI MS: m/z: 285.24 [M^+], 254.10, 219.43, 205.26, 62.51 (100%).

3h IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 1.10 and 1.23 (3H, two t, N–O–CH_2–CH_3), 4.12 and 4.22 (2H, two q, N–O–CH_2–CH_3), 6.36 (1H, s, Ar–H), 7.04–7.54 (8H, m, Ar–H).



Scheme 1.

Table 1
Some characteristics of the compounds

Comp.	M.p. (°C)	Yield (%)	Formulae	Molecular weight
2a	122–124 [a]	75	$C_{15}H_{11}NO_2$	237.2
2b	162–165	80	$C_{16}H_{13}NO_2$	251.2
2c	154–156	72	$C_{16}H_{13}NO_3$	267.2
2d	166–169	82	$C_{15}H_{10}ClNO_2$	271.6
3a	[b]	52	$C_{16}H_{13}NO_2$	251.2
3b	[b]	58	$C_{17}H_{15}NO_2$	265.2
3c	[b]	68	$C_{17}H_{15}NO_2$	265.2
3d	[b]	70	$C_{18}H_{17}NO_2$	279.3
3e	114–116	68	$C_{17}H_{15}NO_3$	281.2
3f	97–99	62	$C_{18}H_{17}NO_3$	295.3
3g	121–123	72	$C_{16}H_{12}ClNO_2$	285.7
3h	122–123	70	$C_{17}H_{14}ClNO_2$	299.7
4a	67–69	45	$C_{22}H_{17}NO_2$	327.3
4b	71–72	55	$C_{22}H_{16}ClNO_2$	361.8
4c	109–110	48	$C_{23}H_{19}NO_2$	341.3
4d	95–97	60	$C_{23}H_{18}ClNO_2$	375.8
4e	108–109	52	$C_{23}H_{19}NO_3$	357.3
4f	88–90	65	$C_{23}H_{18}ClNO_3$	391.8
4g	132–133	48	$C_{22}H_{16}ClNO_2$	361.8
4h	136–137	55	$C_{22}H_{15}Cl_2NO_2$	396.2
5a	141–143	65	$C_{17}H_{13}NO_3$	279.2
5b	69–71	60	$C_{22}H_{15}NO_3$	341.3
5c	104–106	40	$C_{18}H_{15}NO_3$	293.3
5d	80–82	62	$C_{23}H_{17}NO_3$	355.3
5e	87–89	55	$C_{18}H_{15}NO_4$	309.3
5f	102–103	55	$C_{23}H_{17}NO_4$	371.3
5g	99–101	65	$C_{17}H_{12}ClNO_3$	313.7
5h	98–100	58	$C_{22}H_{14}ClNO_3$	375.7

[a] Lit. m.p. 118 °C [7].
[b] Oily.

2.3. Aryl(benzofuran-2-yl)ketoxime ethers (4)

The suitable aryl(benzofuran-2-yl)ketoxime (**2**), (2 mmol), an appropriate alkylhalide (benzyl bromide or 4-chlorobenzylchloride) (2 mmol) and potassium carbonate (2 mmol) were refluxed in acetone for 8 h. The solvent was evaporated and the residue was washed and crystallised from ethanol.

4d IR (KBr) ν_{max} (cm^{-1}): 1635–1515 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.02 and 2.17 (3H, two s, Ar–CH_3), 5.02 and 5.17 (2H, two s, Ar–CH_2–), 7.06–7.60 (13H, m, Ar–H).

4f IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.82 (3H, s, Ar–OCH_3), 5.24 and 5.35 (2H, two s, Ar–CH_2–), 6.78 (1H, s, Ar–H), 7.01–7.78 (12H, m, Ar–H).

4g IR (KBr) ν_{max} (cm^{-1}): 1620–1495 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.07 and 5.21 (2H, two s, Ar–CH_2–), 7.01–7.62 (14H, m, Ar–H).

4h IR (KBr) ν_{max} (cm^{-1}): 1645–1500 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 5.10 and 5.20 (2H, two s, Ar–CH_2–), 6.79 (1H, s, Ar–H), 7.16–7.75 (12H, m, Ar–H), EI MS: m/z: 396.40 [M^+], 364.00, 292.81, 175.14, 124.26 (100%).

2.4. Aryl(benzofuran-2-yl)ketoxime acetates (5a,c,e,g)

The suitable aryl(benzofuran-2-yl)ketoxime (**2**), was refluxed with an excess of acetic anhydride for 1 h. The reaction mixture was poured into water and neutralised with sodium bicarbonate solution. The precipitate formed was filtered and crystallised from ethanol.

5a IR (KBr) ν_{max} (cm^{-1}): 1640–1490 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.00 and 2.10 (3H, two s, N–O–$COCH_3$), 6.79 (1H, s, Ar–H), 7.16–7.75 (9H, m, Ar–H), EI MS: m/z: 279.05 [M^+], 236.86, 42.83 (100%).

5c IR (KBr) ν_{max} (cm^{-1}): 1625–1510 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 2.12 and 2.33 (3H, two s, Ar–CH_3), 3.85 and 3.86 (3H, two s, N–O–$COCH_3$), 6.95–7.80 (9H, m, Ar–H).

2.5. Aryl(benzofuran-2-yl)ketoxime benzoates (5b,d,f,h)

The suitable aryl(benzofuran-2-yl)ketoxime (**2**), (2 mmol) and benzoic anhydride (3 mmol) were refluxed in tetrahydrofurane for 2 h. The solvent was evaporated. The precipitate formed was crystallised from ethanol.

5b IR (KBr) ν_{max} (cm^{-1}): 1625–1510 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 7.22–7.84 (15H, m, Ar–H).

5f IR (KBr) ν_{max} (cm^{-1}): 1625–1510 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 3.92 (3H, s, Ar–OCH_3), 7.15–7.80 (14H, m, Ar–H).

5h IR (KBr) ν_{max} (cm^{-1}): 1638–1510 (C=N, C=C), ^1H NMR (400 MHz) (DMSO-d_6) δ (ppm): 7.21–7.86 (14H, m, Ar–H), EI MS: m/z: 375.65 [M^+], 253.90, 104.65 (100%).

3. Antifungal activity

All the compounds were evaluated in vitro for antifungal activity. Antifungal susceptibility testing was done by using macrobroth dilution test, in accordance with the National Committee for Clinical Laboratory Standards [8]. Results are given as minimal inhibitory concentrations (MIC) in μg/ml in Table 2.

4. Results and discussion

4.1. Chemistry

Aryl(benzofuran-2-yl)ketoxime derivatives were synthesised as outlined in the scheme. The ketones, **1**, were obtained in Modified Rap–Störmer reaction condition [6]. *O*-Alkylketoximes were obtained by using two different methods. While ketones were reacted with *O*-methyl or *O*-ethyl-hydroxylamine in the first method, in

Table 2
Antifungal activities of the compounds (μg/ml)

Comp.	*C. albicans*	Comp.	*C. albicans*
2a	0.5	**4e**	16
2b	2	**4f**	16
2c	2	**4g**	32
2d	4	**4h**	8
3a	2	**5a**	4
3b	4	**5b**	4
3c	1	**5c**	8
3d	4	**5d**	4
3e	2	**5e**	64
3f	4	**5f**	8
3g	2	**5g**	16
3h	1	**5h**	16
4a	16	O	1
4b	16	C	2
4c	16	F	1
4d	16		

O, Oxiconazole; C, Clotrimazol; F, Fluconazole.

the second method, oxime derivatives, **2**, were reacted with benzylbromide or 4-chlorobenzylchloride. Acetates or benzoates, **5**, were prepared by reacting **2** with acetic anhydride or benzoic anhydride, respectively. As expected the presence of *E* and *Z* isomers of the oxime derivatives was confirmed by thin layer chromatography and NMR spectra. Thus, in the NMR spectra aliphatic protons resonated in two different groups with corresponding integral values. However, aromatic protons were observed as multipled peaks.

4.2. Antifungal activity

Antifungal activity tests were performed by macrobroth dilution method using *Candida albicans* strains. Three antifungal agents i.e. oxiconazole, clotrimazole and fluconazole were used as control. The MIC values obtained for these control compounds are 1, 2 and 1 μg/ml, respectively. In consideration of the results we may conclude that some of our products have noticeable antifungal activity. Some of our compounds' MIC values are determined as 1 or 2 μg/ml which is almost equal to those of the controls'. Nevertheless, the most significant compound is appeared to be **2a** with a MIC value lower than the control, i.e. 0.5 μg/ml. Highly effective compounds, **2a**–**d** and **3a**–**h**, should be characterised as, non-substituted or substituted with a small alkyl group on the oxime residue. As mentioned above, the lowest MIC value obtained from the compound **2a**, which has the simplest structure of its group in analogy with this generalisation. However, this relationship could not be observed in oxime esters of acetyl and benzoyl derivatives.

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