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# Synthesis and antifungal activity of novel 1-(1*H*-benzoimidazol-1-yl)propan-2-one oxime-ethers containing the morpholine moiety

**Shaofang Zhou · Fubo Li · Peizhi Zhang · Lin Jiang**

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**Abstract** A series of 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one oxime-ethers have been synthesized from 2-chloromethyl-1*H*-benzoimidazole, morpholine, bromoacetone, hydroxylamine, and a haloalkane (or benzyl halide). Their structures were elucidated by IR, $^{1}$H NMR, elemental analysis, and MS. Antifungal activity against *Botrytis cinerea*, *Sclerotinia sclerotiorum*, and *Beans sclerotia* was evaluated by the mycelium growth-rate method; the results indicated that many of the target compounds have excellent antifungal activity, even higher than that of the control fungicide (carbendazim).

**Keywords** Benzimidazole · Oxime-ether · Morpholine · Synthesis · Antifungal activity

## Introduction

Benzimidazole derivatives have a broad range of biological activity, for example antifungal [1], antibacterial [2], antiviral [3], antitumor [4], and antiparasitic [5], and thus are extensively used in agriculture and as pharmaceuticals. For example, approximately twenty benzimidazole fungicides including carbendazim, benomyl, and thiabendazole have been developed [6]. In addition, a series of 2-substituted benzimidazole compounds containing the oxime-ether moiety were synthesized and evaluated for their antifungal activity in our previous research [7]. The results showed many had high activity.

S. Zhou · P. Zhang · L. Jiang (✉)
College of Chemistry and Material Science, Shandong Agricultural University, Tai'an 271018, China
e-mail: jiangl@sdau.edu.cn

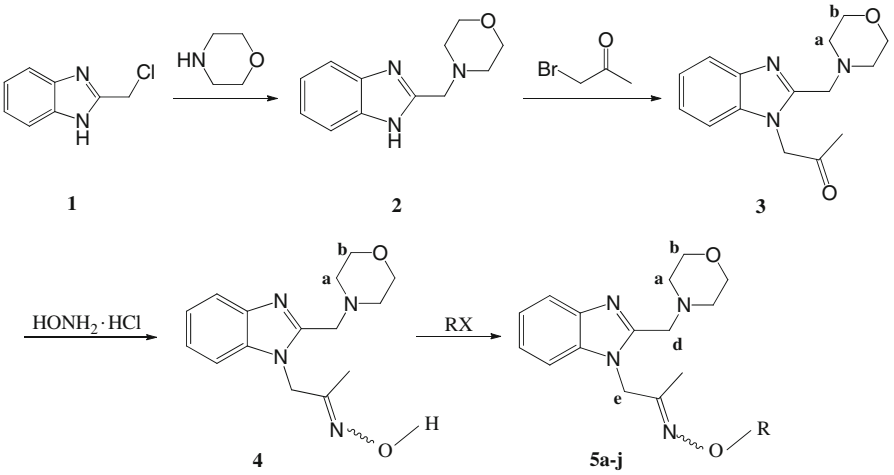
F. Li
College of Plant Protection, Shandong Agricultural University, Tai'an 271018, China

Oxime-ether derivatives have attracted much attention because of their widespread biological activity, for example insecticidal [8], fungicidal [9], and herbicidal [10]. For example, pyrifenox and dimoxystrobin are both efficient oxime-ether fungicides [11, 12]. Moreover, the morpholine ring is a traditional and promising heterocycle with excellent bioactivity, and is often present in compounds used in agriculture. In recent years, many excellent morpholine fungicides, for example dimethomorph and fenpropimorph, have been developed and introduced as commercial pesticides [13]. Motivated by these findings, and in continuation of our interest in the synthesis and bioactivity of benzimidazole derivatives, we designed and synthesized a series of benzimizdazol-1-yl propan-2-one oxime-ethers containing the morpholine moiety, and evaluated their activity against three fungi. The synthetic pathway is shown in Scheme 1.

## Experimental section

Melting points were recorded on an X-5 melting point apparatus with microscope and are uncorrected. IR spectra were recorded on a Shimadzu IR-440 infrared spectrophotometer, as KBr disks or $CHCl_3$ films. $^1H$ NMR spectra were recorded on a Bruker AM-400 spectrometer with $CDCl_3$ as solvent and TMS as internal standard, chemical shifts are reported in ppm (parts per million) values. APCI–MS spectra were acquired on a Micro Mass Agilent 6410 spectrometer. Elemental analysis was performed with an Elementary Vario EL III analyzer.

The intermediates 2-chloromethyl-1*H*-benzimidazole **1** and 2-(4-morpholinomethyl)-1*H*-benzimidazole **2** were prepared in our laboratory in accordance with Ref. [14]. All other solvents and chemicals were of reagent grade and were used without further purification.




**Scheme 1** Synthetic route to the target compounds **5a–j**

Synthesis of 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one **3**

Bromoacetone (1.63 g, 12 mmol) in acetone (5 mL) was added dropwise at room temperature to a stirred mixture of **2** (2.18 g, 10 mmol) and anhydrous potassium carbonate (1.66 g, 12 mmol) in acetone (20 mL). The reaction mixture was then heated under reflux, with stirring, for 7 h until the starting materials had been consumed. The mixture was left to cool, and the precipitate was isolated by filtration and washed with acetone. The filtrate was evaporated under reduced pressure to remove the solvent and a brown solid was obtained. This was recrystallized from ethyl acetate–hexane to give the intermediate **3** as colorless needle crystals. Yield 85 %; mp 180–181 °C. $^1$H NMR (400 MHz, $CDCl_3$): 2.23 (s, 3H, $CH_3$), 2.47 (m, 4H, $H_a$), 3.60 (m, 4H, $H_b$), 3.77 (s, 2H, $H_d$), 5.03 (s, 2H, $H_e$), 7.16–7.76 (m, 4H, ArH); IR (KBr) *v*: 3040, 1726, 1686, 1618, 1111 cm$^{-1}$. Anal. calcd for $C_{15}H_{19}N_3O_2$: C, 65.92; H, 6.95; N, 15.37; Found: C, 65.68; H, 6.85; N, 15.60.

Synthesis of 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one oxime **4**

A mixture of **3** (1.00 g, 4 mmol) and hydroxylamine hydrochloride in 50 % ethanol solution (10 mL) was stirred at room temperature for 15 min, then KOH (0.56 g, 12 mmol) in water (2 mL) was added dropwise, followed by reaction for another 5 h. After completion of the reaction, the solid was collected by filtration, washed with water, dried, and purified by recrystallization from EtOH–$H_2O$ to yield compound **4** as pale yellow crystals. Yield 82 %; mp 223–225 °C. $^1$H NMR (400 MHz, $CDCl_3$): 1.57 (s, 0.64H, $CH_3$, *Z* isomer), 1.85 (s, 2.36H, $CH_3$, *E* isomer), 2.46–2.48 (t, 3.15H, $J = 4.4$ Hz, $H_a$, *E* isomer), 2.54–2.57 (t, 0.85H, $J = 4.4$ Hz, $H_a$, *Z* isomer), 3.60–2.63 (m, 3.15H, $H_b$, *E* isomer), 3.64–3.67 (t, 0.85H, $H_b$, *Z* isomer), 3.74 (s, 1.55H, $H_d$, *E* isomer), 3.78 (s, 0.45H, $H_d$, *Z* isomer), 5.03 (s, 1.58H, $H_e$, *E* isomer), 5.24 (s, 0.42H, $H_e$, *Z* isomer), 7.24–7.76 (m, 4H, ArH, $Z + E$ isomers), 8.93 (s, 0.20H, OH, *Z* isomer), 9.05 (s, 0.80H, OH, *E* isomer); IR (KBr) *v*: 3416, 3060, 1625, 1613, 1132, 1012 cm$^{-1}$. Anal. calcd for $C_{15}H_{20}N_4O_2$: C, 62.49; H, 6.99; N, 19.43. Found: C, 62.65; H, 6.74; N, 19.30.

General procedure for synthesis of 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one oxime-ethers **5a–j**

A mixture of **4** (10 mmol) and KOH (0.56 g, 12 mmol) in ethanol (10 mL) was stirred at room temperature for 15 min, then haloalkane or benzyl halide (12 mmol) in ethanol (10 mL) was added dropwise. The reaction mixture was heated under reflux with stirring for 5–7 h until the reaction was complete. After filtration to remove the resulting precipitate, the filtrate was evaporated on a rotary evaporator. The oil was collected and purified by flash column chromatography on silica gel with 1:3 (*v*/*v*) ethyl acetate–petroleum ether (bp 60–90 °C) as eluent to give the target compounds **5a–j**.

*O-Methyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5a***

Pale yellow crystals; yield: 52 %; mp 115–117 °C. $^1$H NMR (400 MHz, $CDCl_3$): 1.73 (s, 3H, $CH_3$), 2.54–2.56 (t, $J = 4.4$ Hz, 4H, $H_a$), 3.66–3.69 (t, $J = 4.4$ Hz 4H, $H_b$), 3.76 (s, 2H, $H_d$), 3.82 (s, 3H, $OCH_3$), 5.02 (s, 2H, $H_e$), 7.26–7.75 (m, 4H, ArH); IR (KBr) *v*: 3056, 1614, 1519, 1116, 1059 cm$^{-1}$. Anal. calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53; Found: C, 63.78; H, 7.25; N, 18.82; APCI–MS *m/z*: 303.4 $[M + H]^+$.

*O-Ethyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5b***

Yellow oil; yield: 59 %. $^1$H NMR (400 MHz, $CDCl_3$): 1.25–1.28 (t, $J = 7.2$ Hz, 2.36H, $OCH_2C\mathbf{H}_3$, *E* isomer), 1.34 (t, $J = 7.2$ Hz, 0.64H, $OCH_2C\mathbf{H}_3$, *Z* isomer), 1.54 (s, 0.65H, $CH_3$, *Z* isomer), 1.74 (s, 2.35H, $CH_3$, *E* isomer), 2.54–2.56 (m, 4H, $H_a$, *Z* + *E*-isomers), 3.67–3.70 (m, 4H, $H_b$, *Z* + *E* isomers), 3.82 (s, 1.54H, $H_d$, *E* isomer), 3.77 (s, 0.46H, $H_d$, *Z* isomer), 4.10–4.16 (q, $J = 7.2$ Hz, 1.54H, $OC\mathbf{H}_2CH_3$, *E* isomer), 4.18–4.24 (q, $J = 7.2$ Hz, 0.46H, $OC\mathbf{H}_2CH_3$, *Z* isomer), 5.03 (s, 1.57H, $H_e$, *E* isomer), 5.25 (s, 0.43H, $H_e$, *Z* isomer), 7.23–7.77 (m, 4H, ArH, *Z* + *E* isomers); IR ($CHCl_3$) *v*: 3051, 1613, 1519, 1116, 1051 cm$^{-1}$; Anal. calcd for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71; Found: C, 64.25; H, 7.90, N, 17.85; APCI–MS *m/z*: 317.2 $[M + H]^+$.

*O-Propyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5c***

Yellow crystals; yield: 56 %; mp 163–167 °C. $^1$H NMR (400 MHz, $CDCl_3$): 0.84–0.88 (t, $J = 7.2$ Hz, 2.67H, $O(CH_2)_2C\mathbf{H}_3$, *E* isomer), 0.97–1.00 (t, $J = 7.2$ Hz, 0.33H, $O(CH_2)_2C\mathbf{H}_3$, *Z* isomer), 1.53–1.56 (m, 1.75H, $OCH_2C\mathbf{H}_2CH_3$, *E* isomer), 1.55 (s, 0.38H, $CH_3$, *Z* isomer), 1.56–1.60 (m, 0.25H, $OCH_2C\mathbf{H}_2CH_3$, *Z* isomer), 1.87 (s, 2.62H, $CH_3$, *E* isomer), 2.80 (m, 0.50H, $H_a$, *Z* isomer), 2.90 (m, 3.50H, $H_a$, *E* isomer), 3.81 (m, 0.50H, $J = 4.4$ Hz, $H_b$, *Z* isomer), 3.83 (t, $J = 4.4$ Hz, 3.50H, $H_b$, *E* isomer), 3.89 (t, $J = 6.8$ Hz, 1.75H, $OC\mathbf{H}_2C_2H_5$, *E* isomer), 4.11 (t, $J = 6.8$ Hz, 0.25H, $OC\mathbf{H}_2C_2H_5$, *Z* isomer), 4.29 (s, 2H, $H_d$, *Z* + *E* isomers), 5.23 (s, 1.8H, $H_e$, *E* isomer), 5.37 (s, 0.20H, $H_e$, *Z* isomer), 7.41–7.89 (m, 4H, ArH, *Z* + E-isomers); IR (KBr) *v*: 3060, 1613, 1116, 1064 cm$^{-1}$; Anal. calcd for $C_{18}H_{26}N_4O_2$: C, 65.43; H, 7.93; N, 16.96; Found: C, 65.39; H, 8.12; N, 16.79; APCI–MS *m/z*: 331.5 $[M + H]^+$.

*O-Isopropyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5d***

Yellow oil; yield: 73 %. $^1$H NMR (400 MHz, $CDCl_3$): 1.24 (d, $J = 6.4$ Hz, 4.80H, $OCH(C\mathbf{H}_3)_2$, *E* isomer), 1.30 (d, $J = 6.4$ Hz, 1.20H, $OCH(C\mathbf{H}_3)_2$, *Z* isomer), 1.54 (s, 0.63H, $CH_3$, *Z* isomer), 1.73 (s, 2.37H, $CH_3$, *E* isomer), 2.54–2.56 (m, 4H, $H_a$,

$Z + E$ isomers), 3.67–3.69 (m, 4H, $H_b$, $Z + E$ isomers), 3.77 (s, 0.45H, $H_d$, $Z$ isomer), 3.82 (s, 1.55H, $H_d$, $E$ isomer), 4.31 (m, 0.80H, OC**H**$(CH_3)_2$, $E$ isomer), 4.40 (m, 0.20H, OC**H**$(CH_3)_2$, $Z$ isomer), 5.03 (s, 1.60H, $H_e$, $E$ isomer), 5.25 (s, 0.40H, $H_e$, $Z$ isomer), 7.24–7.75 (m, 4H, ArH, $Z + E$ isomers); IR ($CHCl_3$) $v$: 3056, 1617, 1116, 1009 $cm^{-1}$; Anal. calcd for $C_{18}H_{26}N_4O_2$:C, 65.43; H, 7.93; N, 16.96, Found: C, 65.27; H, 8.04; N, 17.20; APCI–MS $m/z$: 331.3 $[M + H]^+$.

*O-Butyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5e***

Pale yellow crystals; yield: 62 %; mp 84–85 °C. $^1$H NMR (400 MHz, $CDCl_3$): 0.92–0.99 (m, 3H, $O(CH_2)_3C\mathbf{H}_3$, $Z + E$ isomers), 1.35–1.41 (m, 2H, $O(CH_2)_2C\mathbf{H}_2CH_3$, $Z + E$-isomers), 1.39 (s, 0.29H, $CH_3$, $Z$ isomer), 1.64 (m, 2H, $O(CH_2)_2C\mathbf{H}_2CH_3$, $Z + E$ isomers), 1.73 (s, 2.71H, $CH_3$, $E$ isomer), 2.55 (m, 4H, $H_a$, $Z + E$ isomers), 3.68 (m, 4H, $H_b$, $Z + E$ isomers), 3.77 (s, 0.25H, $H_d$, Z-isomer), 3.82 (s, 1.75H, $H_d$, $E$ isomer), 4.06–4.10 (t, $J = 6.8$ Hz, 1.80H, OC**H**$_2C_3H_7$, $E$ isomer), 4.14–4.18 (t, $J = 6.8$ Hz, 0.20H, OC**H**$_2C_3H_7$, $Z$ isomer), 5.03 (s, 1.80H, $H_e$, $E$ isomer), 5,25 (s, 0.20H, $H_e$, $Z$ isomer), 7.24–7.76 (m, 4H, ArH, $Z + E$-isomers); IR (KBr) $v$: 3052, 1613, 1117, 1009 $cm^{-1}$; Anal. calcd for $C_{19}H_{28}N_4O_2$: C, 66.25; H, 8.19; N, 16.27; Found: C, 66.49; H, 8.05; N, 16.58; APCI–MS $m/z$: 345.4 $[M + H]^+$.

*O-Benzyl 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5f***

Pale yellow oil; yield: 62 %. $^1$H NMR (400 MHz, $CDCl_3$): 1.54 (s, 0.85H, $CH_3$, $Z$ isomer) 1.78 (s, 2.15H, $CH_3$, $E$ isomer), 2.43–2.49 (m, 4H, $H_a$, $Z + E$ isomers), 3.58–3.64 (m, 4H, $H_b$, $Z + E$ isomers), 3.70 (s, 1.32H, $H_d$, $E$ isomer), 3.72 (s, 0.68H, $H_d$, $Z$ isomer), 5.00 (s, 1.32H, $OCH_2Ar$, $E$ isomer), 5.18 (s, 0.68H, $OCH_2Ar$, $Z$ isomer), 5.09 (s, 1.32H, $H_e$, $E$ isomer), 5.27 (s, 0.68H, $H_e$, $Z$ isomer), 7.18–7.74 (m, 9H, ArH, $Z + E$ isomers); IR ($CHCl_3$) $v$: 3056, 1614, 1116, 1009, 745, 697 $cm^{-1}$; Anal. calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80; Found: C, 69.58; H, 6.74; N, 14.89; APCI–MS $m/z$: 379.5 $[M + H]^+$.

*O-(4-Fluorobenzyl) 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5g***

White crystals; yield: 61 %; mp 82.6–84.7 °C. $^1$H NMR (400 MHz, $CDCl_3$): 1.54 (s, 0.52H, $CH_3$, $Z$ isomer), 1.78 (s, 2.48H, $CH_3$, $E$ isomer) 2.47–2.48 (m, 4H, $H_a$, $Z + E$ isomers), 3.60–3.64 (m, 4H, $H_b$, $Z + E$ isomers), 3.74 (s, 1.68H, $H_d$, $E$ isomer), 3.78 (s, 0.32H, $H_d$, $Z$ isomer), 5.00 (m, 1.68H, $OCH_2Ar$, $E$ isomer), 5.14 (s, 0.32H, $OCH_2Ar$, $E$ isomer), 5.02 (s, 1.68H, $H_e$, $E$ isomer), 5.25 (s, 0.32H, $H_e$, $Z$ isomer), 6.99–7.43 (m, 8H, ArH, $Z + E$ isomers); IR ($CHCl_3$) $v$: 3052, 1604, 1116, 1010, 745 $cm^{-1}$; Anal. calcd for $C_{22}H_{25}FN_4O_2$: C, 66.65; H, 6.36; N, 14.13; Found: C, 66.42; H, 6.16; N, 14.35; APCI–MS $m/z$: 397.4 $[M + H]^+$.

*O-(4-Iodobenzyl) 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5h***

Yellow crystals; yield: 57 %; mp 94–96 °C. $^1$H NMR (400 MHz, $CDCl_3$): 1.53 (s, 0.45H, $CH_3$, *Z* isomer), 1.77 (s, 2.55H, $CH_3$, *E* isomer), 2.47 (m, 4H, $H_a$, *Z* + *E* isomers), 3.64 (m, 4H, $H_b$, *Z* + *E* isomer), 3.71 (s, 2H, $H_d$, *Z* + *E* isomers), 4.99 (s, 1.71H, $OCH_2Ar$, *E* isomer), 5.00 (s, 1.71H, $H_e$, *E* isomer), 5.11 (s, 0.29H, $OCH_2Ar$, *Z* isomer), 5.24 (s, 0.29H, $H_e$, *Z* isomer), 7.01–7.28 (m, 8H, ArH, *Z* + *E* isomers); IR (KBr) *v*: 3051, 1617, 1116, 1007, 745 $cm^{-1}$; Anal. calcd for $C_{22}H_{25}IN_4O_2$: C, 52.39; H, 5.00; N, 11.11; Found: C, 52.28; H, 4.92; N, 11.39; APCI–MS *m/z*: 505.1 $[M + H]^+$.

*O-(4-Chlorobenzyl) 2-(4-morpholinomethyl)-1H-benzimidazol-1-yl acetone oxime-ether* ***5i***

White crystals; yield: 59 %; mp 88–91 °C. $^1$H NMR (400 MHz, $CDCl_3$): 1.54 (s, 0.46H, $CH_3$, *Z* isomer), 1.78 (s, 2.54H, $CH_3$, *E* isomer), 2.46–2.47 (m, 4H, $H_a$, *Z* + *E* isomers), 3.63 (m, 4H, $H_b$, *Z* + *E* isomers), 3.72 (s, 2H, $H_d$, *Z* + *E* isomers), 4.99 (s, 1.72H, $OCH_2Ar$, *E* isomer), 5.02 (s, 1.72H, $H_e$, *E* isomer), 5.13 (s, 0.28H, $OCH_2Ar$, *Z* isomer), 5.25 (s, 0.28H, $H_e$, *Z* isomer), 7.20–7.74 (m, 8H, ArH, *Z* + *E* isomers); IR (KBr) *v*: 3052, 1617, 1117 745 $cm^{-1}$; Anal. calcd for $C_{22}H_{25}ClN_4O_2$: C, 63.99; H, 6.10; N, 13.57; Found: C, 63.74; H, 6.18; N, 13.74; APCI–MS m/z: 413.5 $[M + H]^+$.

*O-(2,4-Dichlorodobenzyl) 1-(2-(4-morpholinomethyl)-1H-benzoimidazol-1-yl)propan-2-one oxime-ether* ***5j***

Yellow oil; yield: 40 %. $^1$H NMR (400 MHz, $CDCl_3$): 1.82 (s, 3H, $CH_3$, *Z* + *E* isomers), 2.47–2.49 (m, 4H, $H_a$, *Z* + *E* isomers), 3.63–3.65 (m, 4H, $H_b$, *Z* + *E* isomers), 3.75 (s, 1.50H, $H_d$, *E* isomer), 3.77 (s, 0.50H, $H_d$, *Z* isomer), 5.0 (s, 1.50H, $OCH_2Ar$, *E* isomer), 5.04 (s, 0.50H, $OCH_2Ar$, *Z* isomer), 5.14 (s, 1.50H, $H_e$, *E* isomer), 5.24 (s, 0.50H, $H_e$, *Z* isomer), 7.20–7.74 (m, 7H, ArH, *Z* + *E* isomers); IR ($CHCl_3$) *v*: 3062, 1615, 1116, 1010, 746 $cm^{-1}$; Anal. calcd for $C_{22}H_{24}Cl_2N_4O_2$: C, 59.07; H, 5.41; N, 12.52; Found: C, 58.92; H, 5.33; N, 12.79; APCI–MS m/z: 447.5 $[M + H]^+$.

## Antifungal activity assays

The in-vitro fungicidal activity of the target compounds **5a–j** against *Beans sclerotia*, *Botrytis cinerea*, and *Sclerotinia sclerotiorum* was evaluated by use of the mycelium growth-rate method [15]. The culture medium was obtained by mixing a solution of **5** with potato dextrose agar (PDA), on which fungus cakes were placed. Culture was performed at 25 ± 1 °C for 96 h. Carbendazim, a commercial fungicide, was used as control, and sterile water was used as blank. Three replicates were performed in antifungal activity assays. Inhibition was expressed as the mean

**Table 1** Antifungal activity as $EC_{50}$ (μg/mL) of the target compounds **5a–j**

| Compound | R | $EC_{50}$ (μg/mL) | | |
|---|---|---|---|---|
| | | *B. Sclerotia* | *B. Cinerea-pers* | *S. Sclerotiorum* |
| **5a** | $CH_3$– | 5.98 ± 1.05 | 0.16 ± 0.12 | 5.86 ± 1.03 |
| **5b** | $CH_3CH_2$– | 14.53 ± 1.27 | 73.84 ± 1.77 | 113.03 ± 1.79 |
| **5c** | $CH_3CH_2CH_2$– | 15.44 ± 1.16 | 15.44 ± 1.21 | 15.31 ± 1.02 |
| **5d** | $(CH_3)_2CH$– | 17.73 ± 1.34 | 64.66 ± 1.35 | 190.98 ± 1.98 |
| **5e** | *n*-$C_4H_9$– | 10.50 ± 1.22 | 7.73 ± 0.78 | 49.30 ± 1.55 |
| **5f** | $C_6H_5CH_2$– | 13.71 ± 1.35 | 56.89 ± 1.45 | 143.77 ± 1.76 |
| **5g** | 4-$FC_6H_4CH_2$– | 8.37 ± 1.26 | 8.69 ± 1.11 | 1.18 ± 0.24 |
| **5 h** | 4-$IC_6H_4CH_2$– | 7.48 ± 1.12 | 7.45 ± 1.17 | 168.42 ± 1.89 |
| **5i** | 4-$ClC_6H_4CH_2$– | 9.21 ± 1.33 | 4.27 ± 0.89 | 1.75 ± 0.16 |
| **5j** | 2,4-$Cl_2C_6H_3CH_2$– | 11.88 ± 1.48 | 40.22 ± 1.88 | 56.65 ± 1.78 |
| Carbendazim | | 3.67 ± 0.76 | 0.18 ± 0.15 | 57.30 ± 1.55 |

*B. sclerotia*, *B. cinerea pers*, and *S. sclerotiorum* are *Beans sclerotia*, *Botrytis cinerea*, and *Sclerotinia sclerotiorum*, respectively

of the values obtained in three independent experiments. Last, effective concentrations ($EC_{50}$) that inhibited mycelium growth by 50 % and toxicity regression equations were also obtained (Table 1). Inhibition was calculated by use of the formula:

$$\text{Inhibition} = \frac{D_0 - D_1}{D_0} \times 100\ (\%)$$

where $D_0$ is the expansion diameter of the mycelia in the blank test, and $D_1$ is the expansion diameter of mycelia in the presence of the tested compounds (Table 1).

## Results and discussion

The synthesis began by treating 2-chloromethyl-1*H*-benzimidazole **1** with morpholine to yield 2-(4-morpholinomethyl)-1*H*-benzimidazole **2**. This was followed by reaction with bromoacetone to give 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one **3**. The intermediate **3** then reacted with hydroxylamine to produce 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one oxime **4**. Last, compound **4** reacts with the haloalkane or benzyl halide to afford the target compound **5**. The structures of **5a–j** were determined by $^1$H NMR, IR, elemental analysis and MS.

## Geometric isomers

There are two geometric isomers, *E* and *Z*, of the target compounds **5b–j** because of the presence of the C=N double bond. However, **5a** has only the *E* isomer, because

$CH_3$ is the smallest alkyl group and there is minimum steric hindrance with another $CH_3$ in the molecule, making the *E* isomer more stable. In the *E* isomers, the alkoxy (or benzyloxy) and benzimidazole moieties are on opposite sides of the C=N bond, so their steric hindrance is smaller. As a result, the *E* isomer is more stable so the amount formed is greater, which was confirmed from the $^1$H NMR spectrum. By measuring the integrated area of the corresponding absorption peak of the same proton in $^1$H NMR [16], it is estimate that the ratios of the two isomers (*Z*/*E*) are from 1.0:2.5 to 1.0:9.3, which means the *E* isomer is the major geometric isomer. For example, the ratios for **5b** (R = $C_2H_5$), **5e** (R = *n*-$C_4H_9$), **5f** (R = $CH_2C_6H_5$), and **5i** (R = $CH_2C_6H_4$Cl-4) are 3.7, 9.3, 2.5, and 5.5, respectively, but there is no good relationship between the ratio and the R group.

## Antifungal activity

As shown in Table 1, the $EC_{50}$ values of the target compounds range from 5.98 to 17.73 μg/mL against *Beans sclerotia*, suggesting moderate to high antifungal activity. However, their activity is lower than that of carbendazim, for which the $EC_{50}$ value is 3.67 μg/mL. Compounds **5a**, **5c**, **5e**, and **5g–i** have good antifungal activity against *Botrytis cinerea* with $EC_{50}$ values of 0.16–8.69 μg/mL; **5a**, especially, has excellent activity, higher than that of carbendazim ($EC_{50}$ = 0.18 μg/mL). Many of the target compounds, for example **5a**, **5c**, **5e**, **5g**, and **5i**, have good activity against *Sclerotinia sclerotiorum*, with $EC_{50}$ values of 1.18–49.30 μg/mL; among these, the $EC_{50}$ values of **5a**, **5g**, and **5i** are much higher than that of carbendazim ($EC_{50}$ = 57.30 μg/mL).

Analysis of the relationship between molecular structure and activity reveals that compounds in which R is $CH_3$, 4-$FC_6H_4CH_2$, or 4-$ClC_6H_4CH_2$, have high activity against the three test fungi.

## Conclusion

In summary, we have synthesized ten novel 1-(2-(4-morpholinomethyl)-1*H*-benzoimidazol-1-yl)propan-2-one oxime-ethers containing the morpholine moiety, by multi-step reactions, with yields of 40–73 %. The structures were determined by IR, $^1$H NMR, MS, and elemental analysis, and the relative amounts of their *Z* and *E* isomers were determined by $^1$H NMR. We also evaluated their in-vitro antifungal activity against *Beans sclerotia*, *Botrytis cinerea*, and *Sclerotinia sclerotiorum*, and found that many of the target compounds have excellent antifungal activity, even higher than that of carbendazim. This study provides a useful reference in the search for novel benzimidazole fungicides.

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