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Efficient synthesis and *in vitro* antifungal activity of 1*H*-benzimidazol-1-yl acetates/propionates containing 1*H*-1,2,4-triazole moiety

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Abstract

A series of novel 1*H*-benzimidazol-1-yl acetates and 1*H*-benzimidazol-1-yl propionates containing 1*H*-1,2,4-triazole moiety were synthesized under microwave irradiation by multi-step reactions, in yields of 87–94%. Their *in vitro* antifungal activities against *Botrytis cinerea* and *Sclerotinia sclerotiorum* were evaluated by mycelial growth rate method. All the target compounds exhibit high activities against *B. cinerea* with the EC_{50} values of 7.96–21.74 μg/mL, higher than that of carbendazim.

Keywords: Benzoimidazole; 1,2,4-Triazole; Synthesis; Antifungal activity

Benzimidazole is an important heterocycle containing two nitrogen atoms, and its derivatives exhibit a broad spectrum of biological activities, such as antifungal, antibacterial, antiviral, antitumor, and antiparasitic activities [1–5]. Thus, benzimidazole derivatives are widely used in agriculture and pharmaceuticals. For example, approximately twenty benzimidazole fungicides including carbendazim, benomyl and thiabendazole have been developed. Due to the high efficiency, broad spectrum and good systemic property, many of this series are still used in the fungicide market [6]. However, owing to the increased resistance of many fungal pathogens, their antifungal activities are significantly reduced. Therefore, it is necessary to develop some novel benzimidazole compounds with low resistance and high activity.

On the other hand, 1,2,4-triazole derivatives display antimicrobial, antifungal, antitumor, anti-inflammatory, and plant growth-regulating activities [7–11], and therefore has been received considerable attention. Up to date, more than thirty 1,2,4-triazole derivatives have been successfully developed commercial agricultural and medical fungicides [12,13], *e.g.* tebuconazole, flusilazole and anastrozole (Fig. 1). Among these fungicide molecules, the 1,2,4-triazole ring and other groups are connected though a methylene or a methenyl, which suggests that the (1,2,4-triazol-1-yl)methyl/methenyl moiety plays an important role in keeping antifungal activity. To the best of our knowledge, the benzimidazole compounds containing the (1,2,4-triazol-1-yl)methyl moiety have not been reported. Motivated by these findings, herein we introduced a (1,2,4-triazol-1-yl)methyl into the benzimidazole ring. Moreover,

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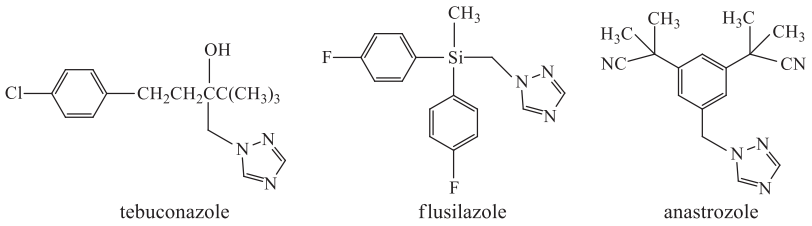


Fig. 1. Chemical structures of some commercial triazole fungicides.

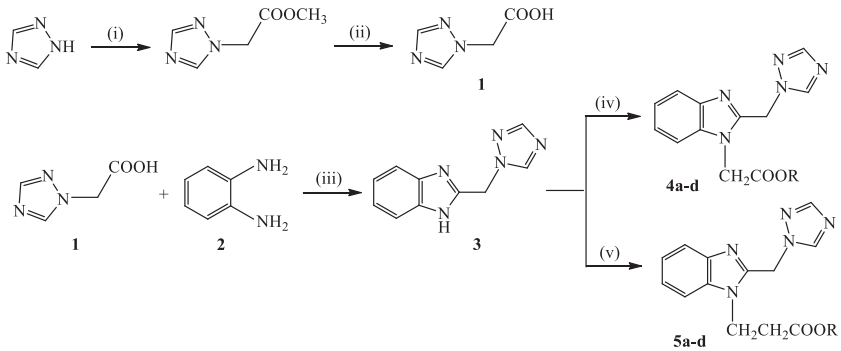
in order to improve the penetrability to pathogen cells, we linked an acetate or a propionate group to the 1-position of the benzimidazole ring. Thus, we designed and synthesized eight novel 2-((1*H*-1,2,4-triazol-1-yl)methyl)-1*H*-benzimidazol-1-yl acetates (**4a–d**) and 3-(2-((1*H*-1,2,4-triazol-1-yl)methyl)-1*H*-benzimidazol-1-yl)propinonates (**5a–d**) under microwave irradiation, and evaluated their antifungal activities against two selected funguses.

The target compounds were synthesized following the described procedure in Scheme 1. The key intermediate 1*H*-1,2,4-triazol-1-yl acetic acid (**1**), was prepared from 1*H*-1,2,4-triazole and methyl chloroacetate referring to the literature [14]. Compound **1** was treated with *o*-phenylenediamine (**2**) in polyphosphoric acid (PPA) under microwave radiation, followed by adjusting the pH to 9.0 with concentrated $NH_3{\cdot}H_2O$, to afford 2-((1*H*-1,2,4-triazol-1-yl)methyl)benzimidazole (**3**) in 87% yield. Finally, **3** was reacted with chloroacetate to yield the target compound **4**, or **3** was reacted with acrylate to give the target compound **5**. Both the two kinds of reactions were performed in CH_3CN under microwave radiation, using anhydrous K_2CO_3 as a base and dibenzo-18-crown-6 as a phase transfer catalyst.

Currently, microwave-assisted synthesis as an effective technique is widely used in chemical reactions. Compared with conventional methods, this technique exhibits many advantages such as higher yield and shorter reaction time [15,16]. Thus, the reactions were carried out by microwave irradiation, which could smoothly afford the target compounds **4** and **5** in yields of 87–94%, whereas the products were obtained in yields of 53–85% under the conventional reflux condition in 4 h. In addition, two ways were employed in the syntheses of the target compounds: **4** was obtained by nucleophilic substitution reaction of **3** with chloroacetate, while **5** was obtained by Michael addition reaction of **3** with acrylate. However, if **5** was synthesized by the substitution reaction of **3** with 3-chloropropionate, the yield was fairly low (30–50%). The reason was that 3-chloropropionate displays a lower reaction activity to the N atom of benzimidazole ring when compared with chloroacetate.

The structures of the target compounds were characterized by IR, NMR, MS and elemental analyses, as shown in Ref. [17].

In vitro antifungal activity of the target compounds **4** and **5** was evaluated by mycelial growth rate method according to the literature [18]. Two kinds of funguses, peas *Botrytis cinerea* and tomato *Sclerotinia sclerotiorum*, were used to the test. Carbendazim, a commercial fungicide, was used as the positive control (*CK*), and sterile water was used as the blank. The inhibition rate was expressed as the mean of values obtained in three independent experiments, and the effective concentration (EC_{50}) that inhibited mycelium growth by 50% was obtained. As seen from Table 1, satisfactory toxicity regression equations were given with the correlation coefficients (*r*) of



Scheme 1. Reagents and conditions: (i) methyl chloroacetate, anhydrous K_2CO_3, CH_3CN, reflux 6 h; (ii) H_2O, reflux 12 h; (iii) PPA, MW. 180 W, 10 min; $NH_3{\cdot}H_2O$; (iv) chloroacetate, anhydrous K_2CO_3, dibenzo-18-crown-6, CH_3CN, MW. 180 W, 10 min, (v) acrylate, anhydrous K_2CO_3, dibenzo-18-crown-6, CH_3CN, MW. 180 W, 10 min.

Table 1
The *in vitro* antifungal activity of the target compounds **3** and **4**.

Entry	*R*	*Botrytis cinerea*			*Sclerotinia sclerotiorum*		
		Regression equations	*r*	EC_{50} (μg/mL)	Regression equations	*r*	EC_{50} (μg/mL)
4a	CH_3	$y = 4.0885x + 0.7168$	0.9689	18.69 ± 1.27	$y = 4.4775x + 0.3502$	0.9890	31.04 ± 1.49
4b	C_2H_5	$y = 3.8902x + 0.8483$	0.9823	20.33 ± 1.31	$y = 4.6581x + 0.2264$	0.9807	32.37 ± 1.51
4c	*n*-C_4H_9	$y = 4.0806x + 0.7926$	0.9611	14.45 ± 1.16	$y = 4.1568x + 0.5610$	0.9916	31.84 ± 1.50
4d	$CH_2C_6H_5$	$y = 4.0421x + 0.7163$	0.9709	21.74 ± 1.34	$y = 4.1257x + 0.6825$	0.9833	19.10 ± 1.28
5a	CH_3	$y = 4.2795x + 0.6036$	0.9943	15.62 ± 1.19	$y = 3.8573x + 0.6522$	0.9935	46.51 ± 1.75
5b	C_2H_5	$y = 4.2795x + 0.6036$	0.9669	7.96 ± 0.90	$y = 4.0346x + 0.7849$	0.9919	16.98 ± 1.23
5c	*n*-C_4H_9	$y = 3.6630x + 1.0806$	0.9809	17.27 ± 1.24	$y = 4.1708x + 0.5371$	0.9907	34.99 ± 1.54
5d	$CH_2C_6H_5$	$y = 3.7482x + 1.0928$	0.9738	13.98 ± 1.14	$y = 4.5170x + 0.4133$	0.9749	14.74 ± 1.67
CK		$y = 3.8794x + 1.9462$	0.9746	30.15 ± 1.60	$y = 4.3606x + 0.9256$	0.9875	4.91 ± 0.69

0.9611–0.9943. On the other hand, the EC_{50} values of the target compounds against *B. cinerea* were ranged from 7.96 to 21.74 μg/mL, less than that of carbendazim, which means compounds **4** and **5** possess high antifungal activities to this kind of pathogen; among them, **5b** exhibits the highest activity. Compared with carbendazim, however, the target compounds showed larger EC_{50} values (14.74–46.51 μg/mL) against *S. sclerotiorum*, suggesting that their activities are lower than that of carbendazim. In addition, it was also found from Table 1, to the same pathogen, there was no significant difference in EC_{50} values between compounds **4** and **5**, indicating that 1*H*-benzimidazol-1-yl acetate and propionate analogue display the similar antifungal activity.

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[17] Analytic data for target compounds. **4a**: white solid, yield: 91%; mp: 173.4–175.2 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 3.74 (s, 3H), 5.18 (s, 2H), 5.68 (s, 2H), 7.27–7.78 (m, 4H), 7.93 (s, 1H), 8.28 (s, 1H); IR (KBr): υ 1736, 1229 cm^{-1}; ESI-MS *m/z*: 272.5 $(M+H)^+$. Anal. Calcd. for $C_{13}H_{13}N_5O_2$: C 57.56, H 4.83, N 25.82; found: C 57.84, H 5.07, N25.49. **4b**: white solid, yield: 94%; mp: 177.8–179.1 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.15 (s, 2H), 5.68 (s, 2H), 7.27–7.34 (m, 4H), 7.93 (s, 1H), 8.28 (s, 1H); IR (KBr): υ 1735, 1220 cm^{-1}; ESI-MS *m/z*: 286.4 $(M+H)^+$. Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C 58.94, H 5.30, N 24.55; found: C 59.22, H 5.08, N 24.35. **4c**: white solid, yield: 93%; mp: 125.4.4–126.1 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.2 Hz), 1.24–1.33 (m, 2H), 1.54–1.69 (m, 2H), 4.13 (t, 2H, *J* = 7.2 Hz), 5.15 (s, 2H), 5.68 (s, 2H), 7.26–7.79 (m, 4H), 7.93 (s, 1H), 8.27 (s, 1H); IR (KBr): υ 1731, 1217 cm^{-1}; ESI-MS *m/z*: 314.6 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{19}N_5O_2$: C 61.33, H 6.11, N 22.35; found: C 61.65, H 6.04, N 22.63. **4d**: white solid, yield: 94%; mp: 152.4–153.6 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 5.17 (s, 2H), 5.20 (s, 2H), 5.64 (s, 2H), 7.26–7.79 (m, 9H), 7.83 (s, 1H), 8.23 (s, 1H); IR (KBr): υ 1725, 1203 cm^{-1}; ESI-MS *m/z*: 348.4 (M+H)+. Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C 65.69, H 4.93, N 20.16; found: C 65.41, H 4.75, N 20.48. **5a**: pale yellow oil, yield: 89%; ^{1}H NMR (400 Hz, $CDCl_3$): δ 2.84 (t, 2H, *J* = 7.2 Hz), 3.60 (s, 3H), 4.63 (t, 2H, *J* = 7.2 Hz), 5.88 (s, 2H), 7.18–7.61

(m, 4H), 7.95 (s, 1H), 8.69 (s, 1H); IR (CCl_4) υ: 1735, 1208 cm^{-1}; ESI-MS *m/z*: 286.5 $(M+H)^+$. Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C 58.94, H 5.30, N 24.55; found: C 58.64, H 5.62, N 24.26. **5b**: yellow oil, yield: 91%; ^1H NMR (400 Hz, CDCl3): δ 1.20 (t, 3H, J = 7.2 Hz), 2.82 (t, 2H, J = 6.4 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.64 (t, 2H, J = 6.4 Hz), 5.84 (s, 2H), 7.28–7.95 (m, 4H), 7.95 (s, 1H), 8.32 (s, 1H); IR (CCl_4) υ: 1732, 1206 cm^{-1}; ESI-MS *m/z*: 300.5 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C 60.19, H 5.72, N 23.40; found: C 60.39, H 5.96, N 23.72. **5c**: yellow oil, yield: 87%; ^1H NMR (400 Hz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.0 Hz), 1.24–1.33 (m, 2H), 1.50–1.57 (m, 2H), 2.83 (t, 2H, J = 7.2 Hz), 4.05 (t, 2H, J = 7.0 Hz), 4.64 (t, 2H, J = 7.2 Hz), 5.84 (s, 2H), 7.28–7.77 (m, 4H), 7.94 (s, 1H), 8.32 (s, 1H); IR (CCl_4) υ: 1731, 1191 cm^{-1}; ESI-MS *m/z*: 328.5 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{21}N_5O_2$: C 62.37, H 6.47, N 21.39; found: C 62.45, H 6.18, N 21.07. **5d**: white solid, yield: 92%; mp: 152.4–153.6 °C; ^1H NMR (400 Hz, $CDCl_3$) δ: 2.88 (t, 2H, J = 6.4 Hz), 4.65 (t, 2H, J = 6.4 Hz), 5.08 (s, 2H), 5.76 (s, 2H), 7.33–7.78 (m, 4H), 7.91 (s, 1H), 8.27 (s, 1H); IR (KBr) υ: 1728, 1187 cm^{-1}; ESI-MS *m/z*: 362.5 $(M+H)^+$. Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C 66.47, H 5.30, N 19.38; found: C 66.28, H 5.49, N 19.13.

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