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Synthesis and Bioactivities of Novel *N*-(4-(2-Aryloxythiazol-5-yl)but-3-yn-2-yl)benzamides

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A series of novel *N*-(4-(2-aryloxythiazol-5-yl)but-3-yn-2-yl)benzamide derivatives were designed and synthesized. Their structures were identified by ^{1}H NMR and elemental analyses. Preliminary bioassays indicated that some title compounds provided ＞80% control of *Sclerotinia sclerotiorum* at 50 μg/mL and ＞70% herbicidal activities against *B. campestris* at 100 μg/mL. Their structure-activities relationships were also discussed.

Keywords fungicides, benzamide, ACCase, aryloxythiazole, herbicide

Introduction

Acetyl-coenzyme A carboxylases (ACCase) were key enzymes in fatty acid biosynthesis in both eukaryotes and prokaryotes[1-3] and attractive targets for drug discovery.[4-6] Recently, *N*-(3-(2-aryloxythiazol-5-yl)-prop-2-ynyl)acetamide (**A**) (Figure 1) was reported as a new kind inhibitor against recombinant human ACCase to provide a safer therapeutic approach for chronic treatment of obesity, diabetes, and other symptoms of the metabolic syndrome.[7,8] Since the human and yeast carboxyl-transferase (CT) domains shared 50% overall amino acid sequence identity, and the sequence conservation was even higher (*ca.* 90%) in the active site region,[5] the further research of **A**'s fungicidal activities may result in the discovery of a new kind of fungicides targeting ACCase and would be helpful to resolve the resistance of other fungicides.

The crystal structures of the CT domain of yeast ACCase in complex with commercial herbicides[9-12] (Figure 2a－2c) and their interactions between them were reported.[13-17] These facts further suggested that the CT domain may be a suitable target for discovering small-molecule inhibitors against ACCase. By docking **A** with the CT domain of yeast ACC, similar mode of interaction was observed (Figure 2d). It was also noticed that many compounds, containing the moiety of substituted benzamide, exhibited excellent fungicidal activities [boscalid,[18] fluopicolide,[19] fluopyram[19] and zoxamide[20] (Figure 1)]. To find potent lead compounds, compounds **B** were designed and synthesized (Scheme 1). Their fungicidal activities were evaluated.

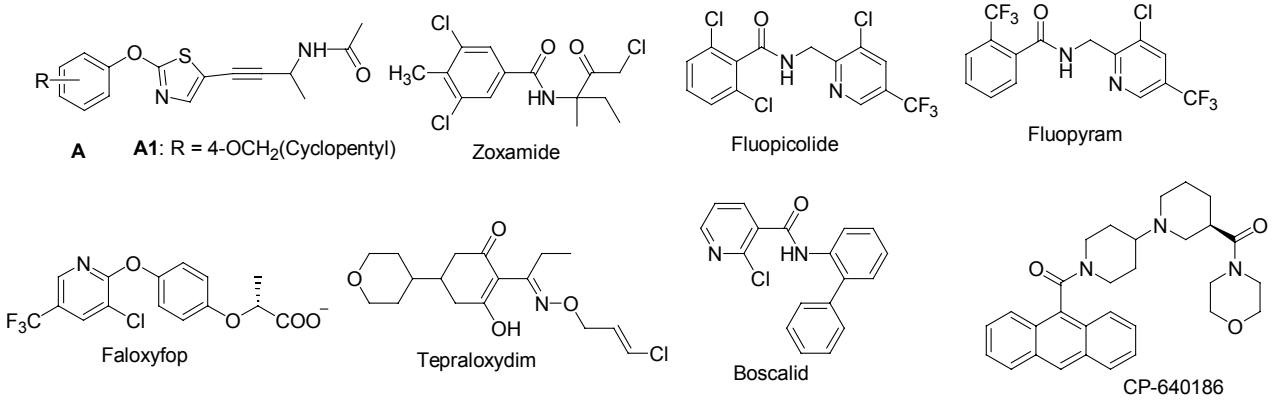

Figure 1 The structures of **A** and some commercial products.

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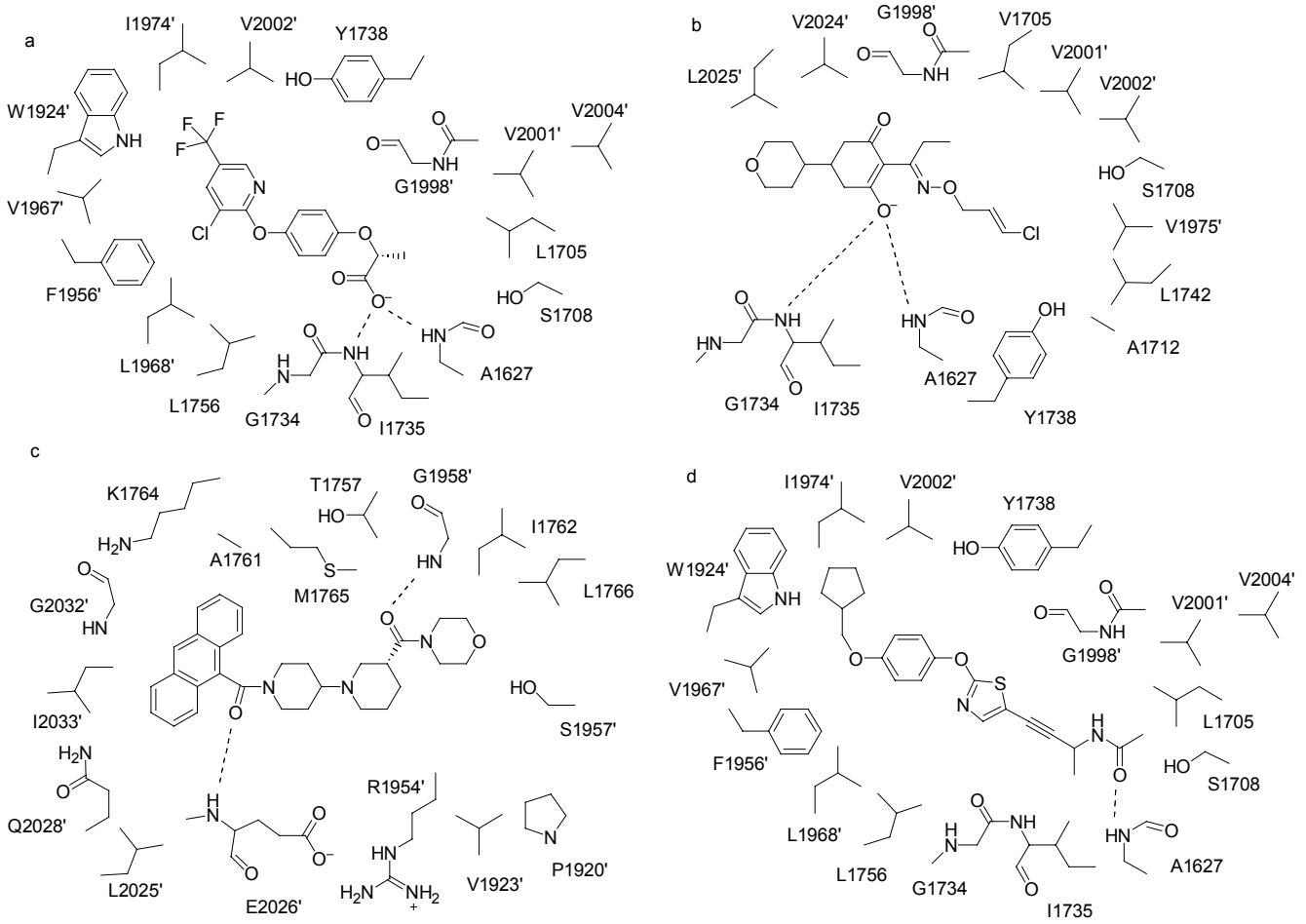
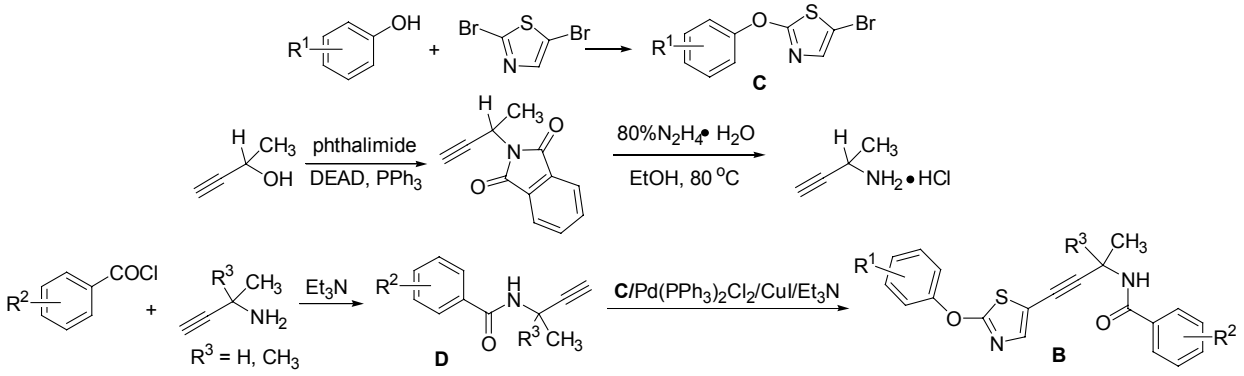


Figure 2 Schematic drawing of the interactions between the CT domain and haloxyfop (a), tepraloxydim (b), **CP-640186** (c) and **A1** (d), respectively.

Scheme 1



Experimental

Synthetic procedures

^{1}H NMR spectra were obtained on 400 MHz (Varian Mercury Plus 400 spectrometer) in $CDCl_3$ solution with tetramethylsilane as the internal standard. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and uncorrected. X-ray diffraction analyses were measured on a Siemens P4 diffractometer. Yields were not optimized. Solvents were dried according to standard methods and distilled prior to use.

General synthetic procedure for C

Compounds **C** were synthesized as the literature described.[9]

Data for C1 (R^1=2-Cl) Yellow liquid, yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.06 (s, 1H), 7.15—7.19 (m, 1H), 7.25—7.27 (m, 2H), 7.40—7.42 (m, 1H).

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Data for C2 (R^1=3-Cl) Colorless liquid, yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09−7.10 (m, 2H), 7.16−7.30 (m, 3H).

Data for C3 (R^1=4-Cl) White solid, yield 94%, m.p. 49−50 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09 (s, 1H), 7.14 (d, J=8.7 Hz, 2H), 7.31 (d, J=8.7 Hz, 2H).

Data for C4 (R^1=3-F) Colorless liquid, yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88−7.00 (m, 3H), 7.11 (s, 1H), 7.27−7.33 (m, 1H).

Data for C5 (R^1=4-F) White solid, yield 95%, m.p. 45−47 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01−7.06 (m, 2H), 7.08 (s, 1H), 7.15−7.19 (m, 2H).

Data for C6 (R^1=4-OCH_3) White solid, yield 72%, m.p. 44−45 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 6.86 (d, J=9.1 Hz, 2H), 7.11 (d, J=8.7 Hz), 7.07 (s, 1H).

Data for C7 (R^1=3-CF_3) Colorless liquid, yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 7.38−7.47 (m, 4H).

Data for C8 (R^1=2,4-Cl_2) White solid, yield 91%, m.p. 76−77 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (s, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

General synthetic procedure for D1−D4

A mixture of 2-(but-3-yn-2-yl)isoindoline-1,3-dione (10 mmol)[21] and 80% hydrazine monohydrate (15 mmol) in 80 mL ethanol was refluxed for 3.5 h. The mixture was cooled, acidified with concentrate hydrochloride and filtered. The filtrate was concentrated to give crude 2-(but-3-yn-2-yl)isoindoline-1,3-dione used for next step without further purification. It was further transformed into compound **D** by reaction with different aroyl chlorides.

Data for D1 (R^2=2-Cl; R^3=H) White solid, total yield 84%, m.p. 91−94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55 (d, J=6.9 Hz, 3H), 2.32 (d, J=2.3 Hz, 1H), 4.95−5.11 (m, 1H), 6.41 (s, 1H), 7.31−7.42 (m, 3H), 7.67−7.69 (m, 1H).

Data for D2 (R^2=4-Cl; R^3=H) White solid, total yield 85%, m.p. 112−114 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (d, J=6.9 Hz, 3H), 2.32 (d, J=2.1 Hz, 1H), 4.93−5.08 (m, 1H), 6.35 (s, 1H), 7.41 (d, J=8.4 Hz, 2H), 7.72 (d, J=8.4 Hz, 2H).

Data for D3 (R^2=2,4-Cl_2; R^3=H) White solid, total yield 87%, m.p. 102−104 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (d, J=6.9 Hz, 3H), 2.32 (d, J=2.1 Hz, 1H), 4.91−5.09 (m, 1H), 6.46 (s, 1H), 7.32 (dd, J=8.3, 1.6 Hz, 1H), 7.42 (d, J=1.6 Hz, 1H), 7.64 (d, J=8.3 Hz, 1H).

Data for D4 (R^2=4-CH_3; R^3=H) White solid, total yield 75%, m.p. 126−129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, J=6.9 Hz, 3H), 2.30 (d, J=2.3 Hz, 1H), 2.39 (s, 3H), 4.93−5.08 (m, 1H), 6.36 (s, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.68 (d, J=8.0 Hz, 2H).

General synthetic procedure for D5−D8

Compounds **D5−D8** were synthesized by reacting 2-methylbut-3-yn-2-amine with different substituted benzoyl chlorides.[22] **D5** (R^2=2-Cl; R^3=4-CH_3), m.p. 95−96 ℃ (94−96 ℃[22]); **D6** (R^2=4-Cl; R^3=4-CH_3): m.p. 144−145 ℃ (141−143 ℃[22]); **D7** (R^2=2,4-Cl_2; R^3=4-CH_3): m.p. 109−110 ℃ (108−109 ℃[22]); **D8** (R^2=4-CH_3; R^3=4-CH_3): m.p. 126−129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (s, 6H), 2.39 (s, 4H, CH_3), 6.20 (s, 1H), 7.22 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.1 Hz, 2H).

General synthetic procedure for B

To a degassed solution of **C** (3 mmol), **D** (3.3 mmol) and triethylamine (15 mmol) in 25 mL of dry THF, were added dichlorobis(triphenylphosphine) palladium (0.015 mmol) and copper iodide (0.006 mmol). After the mixture was refluxed under nitrogen for 3 h, it was cooled to room temperature and poured slowly into 30 mL of saturated ammonia chloride solution. The mixture was extracted with methylene chloride. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel, using ethyl acetate-petroleum ether as the eluent to afford the pure target product **B**.

Data for 2-chloro-*N*-(4-(2-(2-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B1) Yield 44%, m.p. 114−116 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 5.64 (s, 1H), 7.04 (s, 1H), 7.10−7.14 (m, 1H), 7.20−7.29 (m, 3H), 7.32−7.42 (m, 3H), 7.80−7.83 (m, 1H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.28, H 3.67, N 6.46.

Data for 4-chloro-*N*-(4-(2-(2-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B2) Yield 59%, m.p. 183−185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 6H), 5.74 (s, 1H), 7.12 (s, 1H), 7.22−7.26 (m, 1H), 7.32−7.42 (m, 2H), 7.46 (d, J=8.6 Hz, 2H), 7.49−7.51 (m, 1H), 7.99 (d, J=8.6 Hz, 2H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.49, H 3.84, N 6.43.

Data for 2-chloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B3) Yield 43%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55 (s, 6H), 5.74 (s, 1H), 7.17 (s, 1H), 7.19−7.22 (m, 2H), 7.31−7.40 (m, 3H), 7.43−7.47 (m, 1H), 7.50−7.52 (m, 1H), 7.90 (dd, J=1.7, 7.7 Hz, 1H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.38, H 3.91, N 6.37.

Data for 4-chloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B4) Yield 43%, m.p. 118−120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 5.75 (s, 1H), 7.17 (s, 1H), 7.20−7.26 (m, 2H), 7.33−7.37 (m, 2H), 7.46 (d, J=8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.43, H 3.48, N 6.42.

Data for 2,4-dichloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B5) Yield 54%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 1.80 (s, 6H), 6.43 (s, 1H), 7.16－7.18 (m, 1H), 7.23－7.27 (m, 1H), 7.28－7.36 (m, 4H), 7.39 (s, 1H), 7.60 (d, J＝8.3 Hz, 1H). Anal. calcd for $C_{21}H_{15}Cl_3N_2O_2S$: C 54.15, H 3.25, N 6.01; found C 54.05, H 3.30, N 6.09.

Data for 2-chloro-*N*-(4-(2-(4-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B6) Yield 40%, m.p. 102－103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (s, 6H), 5.73 (s, 1H), 7.15 (s, 1H), 7.23 (d, J＝8.9 Hz, 2H), 7.37 (d, J＝8.9 Hz, 2H), 7.37－7.39 (m, 1H), 7.43－7.47 (m, 1H), 7.50－7.52 (m, 1H), 7.89 (dd, J＝1.4, 7.7 Hz, 1H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.31, H 3.80, N 6.46.

Data for 4-chloro-*N*-(4-(2-(4-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B7) Yield 47%, m.p. 133－135 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 6H), 5.66 (s, 1H), 7.06 (s, 1H), 7.17 (d, J＝8.9 Hz, 2H), 7.30 (d, J＝8.9 Hz, 2H), 7.38 (d, J＝8.6 Hz, 2H), 7.90 (d, J＝8.6 Hz, 2H). Anal. calcd for $C_{21}H_{16}Cl_2N_2O_2S$: C 58.48, H 3.74, N 6.49; found C 58.45, H 3.69, N 6.46.

Data for 4-methyl-*N*-(4-(2-(4-chlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B8) Yield 47%, m.p. 141－142 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 2.43 (s, 3H), 5.72 (s, 1H), 7.14 (s, 1H), 7.25－7.30 (m, 4H), 7.39 (d, J＝8.5 Hz, 2H), 7.93 (d, J＝8.5 Hz, 2H). Anal. calcd for $C_{22}H_{19}ClN_2O_2S$: C 64.30, H 4.66, N 6.82; found C 64.00, H 4.49, N 6.71.

Data for 2-chloro-*N*-(4-(2-(2,4-dichlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B9) Yield 19%, m.p. 132－134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 6H), 5.66 (s, 1H), 7.03 (s, 1H), 7.19－7.46 (m, 6H), 7.83－7.85 (m, 1H). Anal. calcd for $C_{21}H_{15}Cl_3N_2O_2S$: C 54.15, H 3.25, N 6.01; found C 54.27, H 3.18, N 5.96.

Data for 4-chloro-*N*-(4-(2-(2,4-dichlorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B10) Yield 49 %; m.p. 174－175 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 6H), 5.67 (s, 1H), 7.02 (s, 1H), 7.18－7.28 (m, 2H), 7.39 (d, J＝8.6 Hz, 2H), 7.41－7.42 (m, 1H), 7.93 (d, J = 8.6 Hz, 2H). Anal. calcd for $C_{21}H_{15}Cl_3N_2O_2S$: C 54.15, H 3.25, N 6.01; found C 54.36, H 3.40, N 5.97.

Data for *N*-(4-(2-(2-chlorophenoxy)thiazol-5-yl)-2-methylbut-3-yn-2-yl)-3-fluorobenzamide (B11) Yield 49%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 5.65 (s, 1H), 6.81－6.86 (m, 1H), 6.94－6.99 (m, 2H), 7.09 (s, 1H), 7.22－7.28 (m, 2H), 7.32－7.36 (m, 1H), 7.39－7.41 (m, 1H), 7.80－7.82 (m, 1H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 60.79, H 3.89, N 6.75; found C 60.54, H 3.81, N 6.61.

Data for *N*-(4-(2-(3-fluorophenoxy)thiazol-5-yl)-2-methylbut-3-yn-2-yl)-4-chlorobenzamide (B12) Yield 58 %, m.p. 106－108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 5.75 (s, 1H), 6.93－6.97 (m, 1H), 7.08－7.12 (m, 2H), 7.18 (s, 1H), 7.34－7.39 (m, 1H), 7.45 (d, J＝8.1 Hz, 2H), 7.98 (d, J＝8.1 Hz, 2H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 60.79, H 3.89, N 6.75; found C 60.99, H 3.74, N 6.76.

Data for *N*-(4-(2-(3-fluorophenoxy)thiazol-5-yl)-2-methylbut-3-yn-2-yl)-2,4-dichlorobenzamide (B13) Yield 46%, m.p. 54－56 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (s, 6H), 6.36 (s, 1H), 6.96－7.08 (m, 3H), 7.30－7.41 (m, 4H), 7.63 (d, J＝8.3 Hz, 1H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 56.13, H 3.36, N 6.23; found C 55.98, H 3.25, N 6.18.

Data for *N*-(4-(2-(3-fluorophenoxy)thiazol-5-yl)-2-methylbut-3-yn-2-yl)-4-methylbenzamide (B14) Yield 42%, m.p. 99－102 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 6H), 2.42 (s, 3H), 5.73 (s, 1H), 6.93－6.97 (m, 1H), 7.07－7.11 (m, 2H), 7.18 (s, 1H), 7.28 (d, J＝7.3 Hz, 2H), 7.34－7.37 (m, 1H), 7.94 (d, J＝7.3 Hz, 2H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 66.99, H 4.85, N 7.10; found C 67.05, H 5.10, N 7.08.

Data for 2-chloro-*N*-(4-(2-(4-fluorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B15) Yield 31%, m.p. 92－94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 6H), 5.62 (s, 1H), 6.53－6.99 (m, 2H), 7.04 (s, 1H), 7.13－7.16 (m, 2H), 7.22－7.26 (m, 1H), 7.30－7.34 (m, 1H), 7.38－7.40 (m, 1H), 7.79 (dd, J＝1.4, 7.7 Hz, 1H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 60.79, H 3.89, N 6.75; found C 61.00, H 3.97, N 6.78.

Data for 4-chloro-*N*-(4-(2-(4-fluorophenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B16) Yield 50%, m.p. 158－159 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 6H), 5.64 (s, 1H), 7.00－7.05 (m, 3H), 7.18－7.21 (m, 2H), 7.36 (d, J＝8.5 Hz, 2H), 7.88 (d, J＝8.5 Hz, 2H). Anal. calcd for $C_{21}H_{15}ClFN_2O_2S$: C 60.79, H 3.89, N 6.75; found C 60.70, H 3.74, N 6.72.

Data for 2-chloro-*N*-(4-(2-(4-methoxyphenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B17) Yield 54%, m.p. 92－94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 6H), 3.74 (s, 3H, OCH_3), 5.64 (s, 1H), 6.85 (d, J＝9.0 Hz, 2H), 7.08 (s, 1H), 7.13 (d, J＝9.0 Hz, 2H), 7.27－7.44 (m, 3H), 7.82－7.84 (m, 1H). Anal. calcd for $C_{22}H_{19}ClN_2O_3S$: C 61.89, H 4.49, N 6.56; found C 61.98, H 4.43, N 6.54.

Data for 4-chloro-*N*-(4-(2-(4-methoxyphenoxy)-thiazol-5-yl)-2-methylbut-3-yn-2-yl)benzamide (B18) Yield 62%, m.p. 117－119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 6H), 3.83 (s, 3H, OCH_3), 5.72 (s, 1H), 6.94 (d, J＝9.0 Hz, 2H), 7.24 (d, J＝9.0 Hz, 2H), 7.44 (d, J＝8.5 Hz, 2H), 7.96 (d, J＝8.5 Hz, 2H). Anal. calcd for $C_{22}H_{19}ClN_2O_3S$: C 61.89, H 4.49, N 6.56; found C 62.00, H 4.33, N 6.50.

Data for 2-chloro-*N*-(2-methyl-4-(2-(3-(trifluoromethyl)phenoxy)thiazol-5-yl)but-3-yn-2-yl)benzamide (B19) Yield 54%, yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 6H), 5.66 (s, 1H), 7.10 (s, 1H), 7.24－7.30 (m, 1H), 7.34－7.49 (m, 6H), 7.80－7.83 (m, 1H). Anal. calcd for $C_{22}H_{16}ClF_3N_2O_2S$: C 56.84, H 3.47, N 6.03; found C 56.93, H 3.42, N 5.96.

Data for 4-chloro-*N*-(2-methyl-4-(2-(3-(trifluoromethyl)phenoxy)thiazol-5-yl)but-3-yn-2-yl)benzamide (B20) Yield 54%, m.p. 131－134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 5.76 (s, 1H), 7.17 (s,

1H), 7.46 (d, *J*=8.6 Hz, 2H), 7.50−7.61 (m, 4H), 7.98 (d, *J*=8.6 Hz, 2H). Anal. calcd for $C_{22}H_{16}ClF_3N_2O_2S$: C 56.84, H 3.47, N 6.03; found C 56.79, H 3.44, N 5.94.

Data for 4-methyl-*N*-(2-methyl-4-(2-(3-(trifluoromethyl)phenoxy)thiazol-5-yl)but-3-yn-2-yl)benzamide (B21) Yield 52%, m.p. 119−120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (s, 6H), 2.45 (s, 3H), 5.77 (s, 1H), 7.19 (s, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.51−7.63 (m, 4H), 7.96 (d, *J*=8.0 Hz, 2H). Anal. calcd for $C_{23}H_{19}F_3N_2O_2S$: C 62.15, H 4.31, N 6.30; found C 61.93, H 4.17, N 6.23.

Data for 2-chloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)but-3-yn-2-yl) benzamide (B22) Yield 52%, m.p. 83−85 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (d, *J*=6.8 Hz, 3H), 5.11−5.32 (m, 1H), 6.46 (d, *J*=7.7 Hz, 1H), 7.17−7.26 (m, 2H), 7.32−7.42 (m, 6H), 7.67−7.69 (m, 1H). Anal. calcd for $C_{20}H_{14}Cl_2N_2O_2S$: C 57.56, H 3.38, N 6.71; found C 57.40, H 3.46, N 6.58.

Data for 4-chloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)but-3-yn-2-yl)benzamide (B23) Yield 34%, m.p. 113−116 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (d, *J*=6.9 Hz, 3H), 4.13−5.38 (m, 1H), 6.61 (d, *J*=7.9 Hz, 1H), 7.16−7.18 (m, 1H), 7.23−7.25 (m, 1H), 7.29−7.36 (m, 3H), 7.39 (d, *J*=8.5 Hz, 2H), 7.74 (d, *J*=8.5 Hz, 2H). Anal. calcd for $C_{20}H_{14}Cl_2N_2O_2S$: C 57.56, H 3.38, N 6.71; found C 57.43, H 3.46, N 6.63.

Data for 2,4-dichloro-*N*-(4-(2-(3-chlorophenoxy)-thiazol-5-yl)but-3-yn-2-yl)benzamide (B24) Yield 60%, m.p. 107−109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (d, *J*=6.9 Hz, 3H), 5.12−5.39 (m, 1H), 6.50 (d, *J*=8.0 Hz, 1H), 7.17−7.20 (m, 1H), 7.24−7.26 (m, 1H), 7.32−7.38 (m, 4H), 7.43 (d, *J*=1.7 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H). Anal. calcd for $C_{20}H_{13}Cl_3N_2O_2S$: C 53.17, H 2.90, N 6.20; found C 52.97, H 3.05, N 6.23.

Data for *N*-(4-(2-(4-chlorophenoxy)thiazol-5-yl)but-3-yn-2-yl)-4-methyl benzamide (B25) Yield 41%, m.p. 125−128 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (d, *J*=6.9 Hz, 3H), 2.40 (s, 3H), 5.17−5.42 (m, 1H), 6.32 (d, *J*=7.9 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 2H), 7.24 (d, *J*=7.8 Hz, 2H), 7.30 (s, 1H), 7.38 (d, *J*=7.8 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H). Anal. calcd for $C_{21}H_{17}ClN_2O_2S$: C 63.55, H 4.32, N 7.06; found C 63.32, H 4.25, N 7.08.

Data for 2-chloro-*N*-(4-(2-(3-fluorophenoxy)-thiazol-5-yl)but-3-yn-2-yl) benzamide (B26) Yield 24%, m.p. 103−104 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59 (d, *J*=6.8 Hz, 3H), 5.13−5.31 (m, 1H), 6.68 (d, *J*=7.6 Hz, 1H), 6.96−7.08 (m, 3H), 7.29−7.40 (m, 5H), 7.62−7.64 (m, 1H). Anal. calcd for $C_{20}H_{14}ClFN_2O_2S$: C 59.93, H 3.52, N 6.99; found C 59.65, H 3.77, N 6.86.

Data for 4-chloro-*N*-(4-(2-(3-fluorophenoxy)-thiazol-5-yl)but-3-yn-2-yl) benzamide (B27) Yield 50%, m.p. 135−137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (d, *J*=6.9 Hz, 3H), 4.14−5.39 (m, 1H), 6.27 (d, *J*=8.0 Hz, 1H), 6.96−7.01 (m, 1H), 7.03−7.09 (m, 2H), 7.33 (s, 1H), 7.35−7.39 (m, 1H), 7.42 (d, *J*=8.5 Hz, 2H), 8.48 (d, *J*=8.5 Hz, 2H). Anal. calcd for $C_{20}H_{14}ClFN_2O_2S$: C 59.93, H 3.52, N 6.99; found C 59.75, H 3.67, N 7.06.

Data for 2,4-dichloro-*N*-(4-(2-(3-fluorophenoxy)-thiazol-5-yl)but-3-yn-2-yl) benzamide (B28) Yield 38%, m.p. 128−129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59 (d, *J*=6.9 Hz, 3H), 5.12−5.39 (m, 1H), 6.54 (d, *J*=7.9 Hz, 1H), 6.95−7.08 (m, 3H), 7.30−7.43 (m, 4H), 7.64 (d, *J* = 8.3 Hz, 1H). Anal. calcd for $C_{20}H_{13}Cl_2FN_2O_2S$: C 55.18, H 3.01, N 6.44; found C 54.89, H 3.28, N 6.39.

Data for 2,4-dichloro-*N*-(4-(2-(3-fluorophenoxy)-thiazol-5-yl)but-3-yn-2-yl) benzamide (B29) Yield 15%, m.p. 99−103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (d, *J*=6.9 Hz, 3H), 2.40 (s, 3H), 5.13−5.38 (m, 1H), 6.32 (d, *J*=7.9 Hz, 1H), 6.96−7.01 (m, 1H), 7.03−7.09 (m, 2H), 7.24 (d, *J*=8.1 Hz, 2H), 7.32 (s, 1H), 7.35−7.41 (m, 1H), 7.69 (d, *J*=8.1 Hz, 2H). Anal. calcd for $C_{21}H_{17}FN_2O_2S$: C 66.30, H 4.50, N 7.36; found C 66.08, H 4.64, N 7.59.

Data for 4-methyl-*N*-(4-(2-(3-(trifluoromethyl)-phenoxy)thiazol-5-yl)but-3-yn-2-yl)benzamide (B30) Yield 24%, m.p. 131−133 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (d, *J*=6.9 Hz, 3H), 2.40 (s, 3H), 5.17−5.42 (m, 1H), 6.34 (d, *J*=7.9 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 2H), 7.31 (s, 1H), 7.48−7.58 (m, 4H), 7.70 (d, *J*=8.0 Hz, 2H). Anal. calcd for $C_{22}H_{17}F_3N_2O_2S$: C 61.39, H 3.98, N 6.51; found C 61.42, H 3.94, N 6.57.

Bioassays

(1) The antifungal activities of all synthesized compounds were tested against seven pathogenic fungi, namely *Alternaria solani*, *Gibberella zeae*, *Phytophthora infestans*, *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Thanatephorus cucumeris* (Frank) Donk and *Phytophthora capsici* by the poison plate technique.[23]

Compounds **B** were dissolved in 1 mL acetone before mixing with 90 mL potato dextrose agar (PDA). The final concentration of compounds **B** in the medium was tested at 50 μg/mL. All kinds of fungi were incubated in PDA at (27±1) ℃ for 4 d to get new mycelium for antifungal assay. Then mycelia dishes of approximately 4 mm diameter were cut from culture medium and one of them was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate aseptically. The inoculated plates were incubated at (27±1) ℃ for 5 d. Acetone in sterile distilled water served as control, while hymexazole served as positive control. For each treatment, three replicates were conducted. The radial growth of the fungal colonies was measured and the data were statistically analyzed. The inhibiting effects of compounds **B** *in vitro* on these fungi were calculated by the formula: I (%) $=[(C-T)/(C-0.4)]\times 100$, where C represented the diameter of fungi growth on untreated PDA, and T represented the diameter of fungi on treated PDA while I meant inhibition rate. The fungicidal activities were summarized in Table 1.

Table 1 The fungicidal activities of compound **B** (Concentration: 50 μg/mL)

	R^1	R^2	R^3	*Alternaria solani*	*Gibberella zeae*	*Phytophthora infestans*	*Sclerotinia sclerotiorum*	*Botrytis cinerea*	*Thanatephorus cucumeris* (Frank) Donk	*Phytophthora capsici*
B1	2-Cl	2-Cl	CH_3	23.1	22.2	17.6	16.4	14.3	57.1	12.5
B2	2-Cl	4-Cl	CH_3	23.1	11.1	11.8	24.6	19.0	57.1	20.8
B3	3-Cl	2-Cl	CH_3	38.5	36.6	22.2	63.4	26.8	12.7	22.2
B4	3-Cl	4-Cl	CH_3	26.9	12.2	3.7	21.1	17.9	8.5	27.8
B5	3-Cl	2,4-Cl_2	CH_3	35.7	27.3	17.6	40.8	13.7	21.7	21.4
B6	4-Cl	2-Cl	CH_3	46.2	36.6	29.6	81.7	32.1	14.1	27.8
B7	4-Cl	4-Cl	CH_3	30.8	24.4	7.4	14.1	26.8	7.0	36.1
B8	4-Cl	4-CH_3	CH_3	42.9	27.3	23.5	39.5	33.3	41.3	14.3
B9	2,4-Cl_2	2-Cl	CH_3	26.9	31.7	3.7	49.3	26.8	7.0	33.3
B10	2,4-Cl_2	4-Cl	CH_3	26.9	24.4	3.7	35.2	17.9	7.0	27.8
B11	3-F	2-Cl	CH_3	53.8	39.0	25.9	56.3	37.5	9.9	13.9
B12	3-F	4-Cl	CH_3	26.9	24.4	3.7	21.1	26.8	7.0	27.8
B13	3-F	2,4-Cl_2	CH_3	35.7	4.5	35.3	39.5	23.5	26.1	28.6
B14	3-F	4-CH_3	CH_3	35.7	31.8	35.3	46.1	35.3	32.6	10.7
B15	4-F	2-Cl	CH_3	34.6	29.3	14.8	35.2	26.8	0.0	13.9
B16	4-F	4-Cl	CH_3	19.2	14.6	3.7	28.2	17.9	4.2	27.8
B17	4-OCH_3	2-Cl	CH_3	15.4	0.0	17.6	32.8	9.5	57.1	12.5
B18	4-OCH_3	4-Cl	CH_3	23.1	5.6	11.8	16.4	19.0	14.3	20.8
B19	3-CF_3	2-Cl	CH_3	30.8	16.7	29.4	57.4	47.6	60.7	25.0
B20	3-CF_3	4-Cl	CH_3	15.4	11.1	11.8	24.6	19.0	42.9	16.7
B21	3-CF_3	4-CH_3	CH_3	35.7	13.6	11.8	9.2	13.7	17.4	25.0
B22	3-Cl	2-Cl	H	28.6	27.3	29.4	72.4	29.4	28.3	21.4
B23	3-Cl	4-Cl	H	14.3	18.2	17.6	13.2	25.5	21.7	25.0
B24	3-Cl	2,4-Cl_2	H	14.3	27.3	17.6	13.2	15.7	21.7	17.9
B25	4-Cl	4-CH_3	H	21.4	27.3	5.9	11.8	25.5	10.9	14.3
B26	3-F	2-Cl	H	35.7	27.3	23.5	85.5	23.5	8.7	17.9
B27	3-F	4-Cl	H	21.4	27.3	11.8	10.5	13.7	21.7	21.4
B28	3-F	2,4-Cl_2	H	28.6	4.5	5.9	11.8	15.7	21.7	14.3
B29	3-F	4-CH_3	H	38.5	18.8	33.3	31.0	32.6	22.7	25.0
B30	3-CF_3	4-CH_3	H	35.7	13.6	5.9	13.2	13.7	10.9	17.9

(2) The herbicidal activities of compounds **B** were determined with *Brassica campestris* L and *Echinochloa crus-galli* (L) Beauv as samples of annual dicotyledonous and monocotyledonous plants, respectively, using a previously reported procedure.[24-27] For all of the bioassay tests, each treatment was repeated three times.

Treatment

The emulsions of compounds **B** were prepared by dissolving them in 100 μL of *N*,*N*-dimethylformamide with the addition of 2 μL Tween 20. The mixture of the same amount of water, *N*,*N*-dimethylformamide, and Tween 20 was used as control.

Inhibition of the root-growth of rape (*Brassica campestris* L)

Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6-cm Petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 15 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 65 h at 28 (±1) ℃. The lengths of 10 rape roots selected from each plate were measured and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds.

Inhibition of the seedling growth of barnyard grass (*Echinochloa crus-galli* (L) Beauv)

Ten *E. crus-galli* seeds were placed into a 50-mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup was placed in a bright room and the seeds were allowed to germi-

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nate for 65 h at 28 (±1) ℃. The heights of the above-ground parts of the seedlings in each cup were measured and the means calculated. The percentage inhibition was used to describe the control efficiency of the compounds.

The herbicidal activities were summarized in Table 2.

Table 2 Herbicidal activity of compounds **B** (*I*/%; concentration: 100 μg/mL)

	B. campestris	*E. crus-galli*		*B. campestris*	*E. crus-galli*
B1	53.3	0	**B16**	0	0
B3	33.4	0	**B17**	27.1	10.0
B5	6.6	25.0	**B18**	0	52.8
B6	57.3	5.0	**B19**	32.1	44.5
B10	18.3	5.0	**B22**	20.6	30.0
B11	70.2	10.0	**B23**	16.9	20.0
B12	0	15.0	**B25**	55.4	15.0
B13	0	5.0	**B26**	29.2	10.0
B15	57.7	10.0	**B27**	10.3	10.0

Results and Discussion

Molecular docking

Autodock 4.2 was used for molecular docking. We re-docked the cocrystal ligands of three ACCs complex (pdb ID: 1UYR, 3H0J, 3PGQ) as training set to get rational docking parameters. Docking experiments were performed in four sets with different grid spacing: 0.375 Å, 0.500 Å, 0.600 Å, 0.700 Å. Number of points in each dimension was set to 126. In each set, grid center was moved for several times to make sure that we got the atomic potential grid of hole protein. Docking simulations were done using the Lamarckian genetic algorithm with: GA runs＝100, Population Size＝200, Quaternion ＝30.0°, Torsion＝30.0°. Other parameters are set to default.[28]

Each ligand can be well re-docked into their own cocrystal protein with grid spacing 0.375 Å and grid box size 18.75 Å×18.75 Å×18.75 Å. However, when all three ligands were docked into 1UYR with grid spacing 0.375 Å and grid box covering all protein, many false positive results were gotten. Docking with other two protein conformations in pdb 3HOJ and 3PGQ, the same results were gotten. In order to minimize false positive, docking experiments were done with different grid spacing. After re-dock training, best results could be gotten with grid spacing 0.600 Å, which meant that with grid spacing 0.600 Å, all crystal ligands were docked to their own binding sites with docking conformation in first cluster (cluster was sorted by binding energy) and these docking conformations were very similar with their crystal conformations (the rmsd between docking conformation and crystal conformation was less than one: diclofop: rmsd＝0.414, ΔG＝–9.07 kcal/mol, same site as haloxyfop; pinoxaden: rmsd＝0.509, ΔG＝–8.83 kcal/mol, same site as Tepraloxydim; compound **2** in 3H0J: rmsd＝0.615, ΔG＝–11.87 kcal/mol, same site as **CP-640186**). With grid spacing 0.600 Å, compound **B26** was docked into pdb 1UYR. The first three docking conformation clusters were selected as positive docking conformation. In first docking cluster, **B26** was binding near the binding site of haloxyfop (Figure 3a), ΔG＝ –11.06 kcal/mol, this conformation suggested that **B26** may be trapped in a hydrophobic area; In the second docking conformation cluster, **B26** was binding in the binding site of haloxyfop (Figure 3b), ΔG＝–10.49 kcal/mol; The third docking conformation cluster shows that **B26** was binding near the binding site of **CP-640186**, again trapped in a hydrophobic area with ΔG＝–9.10 kcal/mol (Figure 3c).

In the first docking conformation, **B26** was docked in a hydrophobic site with two hydrophobic zones, constructed by residues VAL1733-ILE1735-VAL2001, ILE 1593-ILE2033. In the second docking conformation, **B26** was docked in haloxyftop binding site, which was constructed by residues LEU1738-TYR1756-PHE1956-VAL1967-VAL2002, VAL1733-LEU2025. In the third docking conformation, **B26** was docked in another hydrophobic site, construct by residues LEU1756-ILE1762-PHE1956, LEU1777-ILE1782-ILE1903.

Synthesis

Since 2-(but-3-yn-2-yl)isoindoline-1,3-dione had similar solubility in petroleum ether or ethyl ether with triphenylphosphine oxide, it was not easy to be separated from the reaction mixture. Crude 2-(but-3-yn-2-yl)isoindoline-1,3-dione with little triphenylphosphine oxide was firstly extracted with petroleum ether (30－60 ℃) by Soxhlet extractor and then it was purified by flash column chromatography on silica gel, using ethyl acetate-petroleum ether as the eluent.

Because but-3-yn-2-amine shared lower boiling point, it was transformed to crude but-3-yn-2-amine hydrochloride used for next step without further purification. The crude product was transformed into **D1**－**D4** by reacting with aroyl chloride at the presence of triethylamine (Scheme 1).[29,30]

When the ratios of $Pd(PPh_3)_2Cl_2$ and CuI to **D** were decreased from 5% and 2%[31] to 0.5% and 0.2% respectively, Sonogashira coupling of **C** and **D** was proceeded smoothly and the **B**'s yields were not influenced significantly.

Structure-activity relationships

As shown in Table 1, many compounds presented moderate fungicidal activities at 50 μg/mL (Table 1), but the result was not satisfying. In order to explore the reason, **B26**'s crystal structure was determined[32] (Figure 3d) and it was docked into the binding pocket of the crystal structures of the CT domain of yeast ACC's complex with diclofop (pdb ID: 1UYR). The docking result indicated **B26** had similar interaction with the CT domain of 1UYR as **A1**, haloxyfop and tepraloxydim,

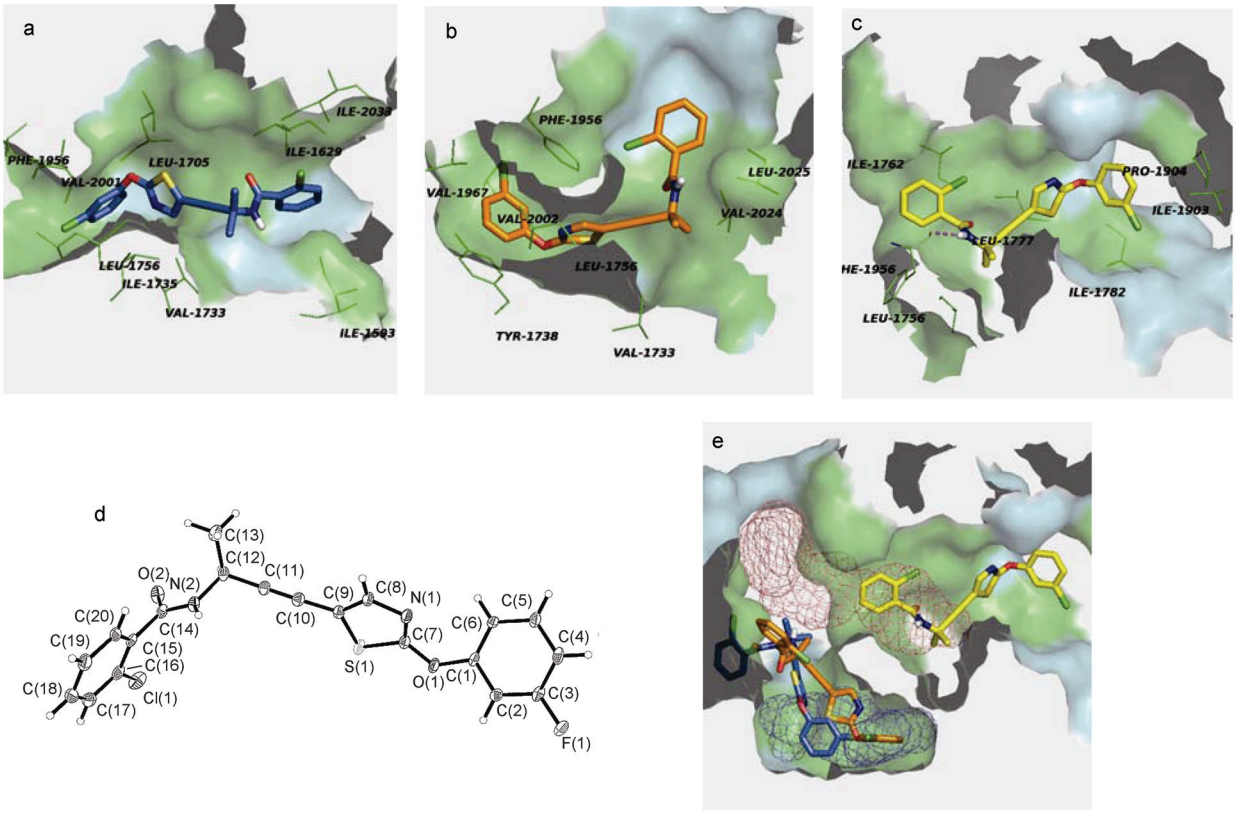

Figure 3 (a) The binding position of **B26** close to the binding position of inhibitor diclofop; (b) docking model of **B26** with the CT domain of yeast ACC; (c) the binding position of **B26** close to the binding position of inhibitor **CP-640186**; (d) the crystal structure of compound **B26**; (e) three binding position of **B26**, the orange one is the ideal binding position, the blue and yellow represent other two possible binding positions, the grids show the binding positions of two co-crystal inhibitors.

but it could not explain the reason why compound **B** did not show excellent fungicidal activities. However, when compound **B26** was docked into 1UYR with grid spacing 0.600 Å and box size 75.6 Å×75.6 Å×75.6 Å which covers most part of protein to detect binding position, it was observed that **B26** adopted three clusters positive docking conformations (Figure 3e) and only part of **B26** was located in the binding pocket. Further analysis demonstrated that two aryl groups for each positive docking conformation bound with two hydrophobic areas (constructed by VAL2001 and ILE1735, ILE2033 and ILE1593 in Figure 3a; constructed by LEU1756 and ILE1762, ILE1782 and ILE1903 and a hydrogen bond with PHE1956 in Figure 3c). From this, it suggested that molecules of **B26** may be trapped by the two hydrophobic areas mentioned above before they got to the binding site of the CT domain. In further, this improper interaction with the CT domain leads to the lower fungicidal activities of **B1**—**B30** and may be the reason why **B1**—**B30** did not possess good herbicidal activities against *B. campestris* and *E. crus-galli* (Table 2).

Conclusions

In this paper, we provide a new chemical scaffold as ACCase inhibitor and reasonable explanation for the observed bioactivity by molecular docking analysis. This would provide a possible way for further structure optimization. Further investigation on lead optimization and fungicidal activities for the compounds is underway in our group.

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