Article

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Design, Synthesis, and Antifungal Evaluation of Novel Benzoxazole Derivatives Containing a 1,2,3-Triazole Moiety

Yu-Qin Jiang,[a] Shu-Hong Jia,[a] Xi-Yong Li,[b] Ya-Min Sun,[b] Wei Li,[a] Wei-Wei Zhang [a*] and Gui-Qing Xu[a*]

[a]*Henan Engineering Laboratory of Chemical Pharmaceuticals and Biomedical Materials, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan, 453007, China*

[b]*Department of Marine Fisheries, Weihai Ocean Vocational College, Weihai, Shandong 264300, China*

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For finding novel bioactive compounds with significant antifungal activities, 17 novel benzoxazole derivatives containing a 1,2,3-triazole moiety were synthesized by the copper(II) acetylacetonate-catalyzed cyclization reaction between 2-aminophenol derivatives and 1*H*-1,2,3-triazole-4-carbaldehyde derivatives (**4a**), which were prepared through three steps using aromatic amine as the starting material. Antifungal activities of the prepared compounds were evaluated against *Botrytis cinerea* (BC) and *Fusarium Verticillium* (FV). The test results indicated that compounds **5b**, **5c**, **5h,** and **5n** show good inhibitory effects on fungi. The preliminary structure–activity relationship is also discussed.

Keywords: Benzoxazole derivatives; Antifungal activity; 1,2,3-Triazole.

INTRODUCTION

Gray mold is a major pathogenic factor during vegetable growth in the world, and is especially harmful for the growth of tomato,[1] strawberry,[2] and onion.[3] Verticillium is a class of fungi distributed all over the world, which can endanger a variety of woody plant roots, causing xylem discoloration, wilting, and falling of leaves.[4] Plant diseases caused by gray mold and verticillium have become a serious problem. To effectively prevent and control plant diseases, fungicides, especially chemical fungicides, are indispensable and crucial.

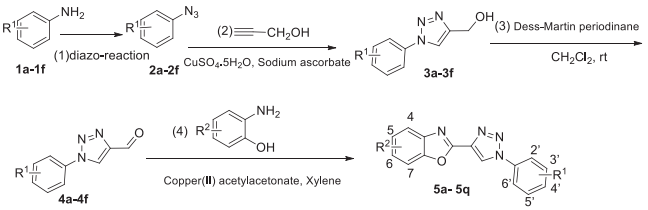
N-Heterocyclic compounds are extraordinarily important compounds that are ubiquitous in vital bioactive molecules and macromolecules. Novel lead compounds in medicinal chemistry are found as hybrids of different heterocyclic scaffolds.[5] Among the various heterocycles, benzoxazoles, and triazoles play an important role in the pharmaceutical and pesticides industries because of their remarkable biological activities, such as antibacterial and antifungal agents,[6,7] cholesteryl ester transfer protein (CETP) inhibitors,[8] antitumor agents,[9,10] anti-inflammatory agents,[11,12] reversible methionine aminopeptidase 2 inhibitors,[13] and anti-HIV-1 agents.[14] The benzoxazole and triazole frameworks have been widely identified as privileged structures or pharmacophores. It has been reported that maleimide, indole, or paeonol connected to 1,2,3-triazole moieties shows potent antitumor activity[15] or antifungal activity.[16–18]

Here, in continuation of our previous research on the synthesis of novel heterocycles, we report the design and synthesis of a series of novel benzoxazole derivatives containing the 1,2,3-triazole framework, to be used as antifungal agents. The antifungal activities of these novel benzoxazole derivatives were evaluated *in vitro* against two plant pathogenic fungi, namely *Botrytis cinerea* (BC) and *Fusarium Verticillium* (FV), using hymexazol as the standard drug.

RESULTS AND DISCUSSION

The general strategy for the synthesis of the target compounds **5a–5q** is illustrated in Scheme 1. Aromatic azides **2a–2f** were prepared from aromatic amines by the diazo reaction.[19] The reaction of **2** with propargyl alcohol gave (1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol

*Corresponding authors. Email: zhangweiwei@htu.edu.cn; guiqingxu@163.com



Scheme 1. Synthesis of compounds **5a–5q**.

derivatives (**3**),[20] which were oxidized by Dess–Martin periodinane to produce 1-phenyl-1*H*-1,2,3-triazole-4-carbaldehyde derivatives (**4**).[21] Then the oxidative cyclization reaction of **4** with 2-aminophenol derivatives catalyzed by 20 mol% copper(II) acetylacetonate ($Cu(acac)_2$) in xylene (3 mL) at 120°C gave the desired compounds **5a**–**5q** with excellent yields (Table 1), which was the key step for the synthesis of the target molecules. The structures of **5a**–**5q** were confirmed by NMR, IR, and high-resolution mass spectroscopy (HRMS).

These novel benzoxazole-linked 1,2,3-triazole derivatives **5a**–**5q** were evaluated *in vitro* for their antifungal activities against two plant pathogenic fungi BC and FV, with hymexazol as the positive control. The inhibition ratios are summarized in Table 1.

As can be seen from Table 1, most of the tested compounds exhibited moderate to high activity against the two tested fungi at 40 μg/mL. Besides, the compounds showed better activity toward BC than FV. Among all the tested compounds, **5b**, **5c**, **5 h**, and **5n** exhibited the best antifungal activity toward BC, which exceeded 80%. In these mentioned structures, when the benzoxazole moiety and benzotriazole were without substituents at aromatic ring, we obtained the best antifungal activity against BC (Table 1, **5b**). However, the benzotriazole moiety containing a 2-CH_3, compounds **5c** and **5n**, showed good inhibitory activity with 81.9% and 81.5% inhibition of BC, respectively (Table 1, **5c**, **5n**). It is worth mentioning that when the benzotriazole moiety had a 3-Cl and the benzoxazole ring had a 5-CH_3, the inhibition ratio was 81.9% as for BC (Table 1, **5h**). Besides, compound **5a**, **5e**–**5g**, and **5j**, with a 2-F or 4-CH_3 group connected to the benzotriazole moiety, showed moderate inhibitory activity toward BC. However, as for FV, only compound **5c** reached 70% inhibition (Table 1, **5c**), probably because of the rapid growth of FV in the beginning. Taking every aspect into consideration, compounds **5b**, **5c**, **5h**, and **5n** are worthy of further investigations, being the most effective compounds in this study.

In conclusion, a series of novel benzoxazole derivatives linked to a 1,2,3-triazole ring system were

Table 1. Target compounds **5a–5q** and their antifungal activity at 40 μg/mL.

Compound	R^1	R^2	Yield (%)	Inhibition ratio[a] (%)	
				BC	FV
5a	4-CH_3	H	91	53.3	31.4
5b	H	H	95	81.9	47.3
5c	2-CH_3	H	91	81.9	70.0
5d	3-Cl	H	92	34.3	38.2
5e	2-F	H	93	53.3	26.8
5f	4-CH_3	5-CH_3	93	53.8	24.5
5g	4-CH_3	4-Cl	94	53.8	24.5
5h	3-Cl	5-CH_3	94	81.9	42.7
5i	2-F	5-CH_3	93	62.9	33.6
5j	2-F	4-Cl	90	53.3	29.1
5k	3-Cl	4-Cl	89	34.3	29.1
5l	4-($COOCH_3$)benzyl	5-CH_3	89	34.3	29.1
5m	2-CH_3	5-CH_3	92	43.8	31.4
5n	2-CH_3	4-Cl	93	81.5	56.4
5o	H	5-CH_3	94	43.8	38.2
5p	H	4-Cl	91	34.3	31.4
5q	4-($COOCH_3$)benzyl	H	88	35.4	29.1
Hymexazol				100	100

[a] Data were collected at 48 h.

designed and synthesized. Most of the target products exhibited good antifungal activity toward BC and FV. Among them, **5b**, **5c**, **5h,** and **5n** were the most promising compounds. These results provide a reference for further study of chemical fungicides.

EXPERIMENTAL

General

All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. The unknown products were characterized using ^{1}H NMR, ^{13}C NMR, melting points, IR spectra, and HRMS. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance (400 MHz) or Bruker AVANCE III HD (600 MHz) spectrometer, with $CDCl_3$ as solvent. Data is represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, q = quartet, m = multiplet), and coupling constants (*J*) are in hertz (Hz). Melting points were determined on a YUHUA X-5 melting point apparatus and are reported uncorrected. IR spectra were recorded on a NEXUS FTIR-Raman spectrometer. HRMS was performed on a MicrOTOF-QII mass spectrometer with an electrospray ionization (ESI) source (Waters, Manchester).

Procedure for the synthesis of compounds 3a–3f

Aryl azide (**2**, 10.0 mmol), propargyl alcohol (10.0 mmol, 560 mg), $CuSO_4{\cdot}5H_2O$ (0.1 mmol, 25 mg), and sodium ascorbate (1.0 mmol, 198 mg) were added to a 100-mL three-necked flask with the solvent (40 mL, methanol/water = 1:1). The reaction was carried out at 55°C for ~1 h. When the reaction was completed, as monitored by TLC, the reaction mixture was concentrated *in vacuo* and the product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4, v:v) as eluent.

Procedure for the synthesis of compounds 4a–4 f

1-Phenyl-1*H*-1,2,3-triazole-4-methanol derivatives (**3**, 5.0 mmol) and the Dess–Martin reagent (6.0 mmol, 1.2 equiv., 2.54 g) were added to a round-bottomed flask. The reaction mixture was stirred at room temperature and monitored by TLC until the raw material was completed consumed. To the above system, 1 M sodium thiosulfate-saturated sodium bicarbonate solution was added until no bubbles were produced. Then the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue obtained was purified by column chromatography on silica gel using ethyl acetate/petroleum ether (1:2, v:v) as eluent.

Procedure for the synthesis of compounds 5a–5q

Aldehydes (**4**, 1.0 mmol), 2-aminophenol derivatives (1.0 mmol), and $Cu(acac)_2$ (0.2 mmol, 52 mg, 20 mol%) were put into a three-necked flask (25 mL) containing xylene (3.0 mL) and equipped with a magnetic stirrer. The reaction mixture was heated to 120°C with stirring. When the starting materials were completely consumed, as determined by TLC analysis, the reaction mixture was concentrated under vacuum and the product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:10, v:v) as eluent.

2-(1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5a). Gray solid. mp 227–228°C. IR (KBr) (ν_{max}, cm^{-1}): 3142 (C—H, Ar), 1646 (C═N), 1589, 1520, 1452 (C—C), 1402 (C—N), 1241 (C—O). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.67 (s, 1H, triazole), 7.79–7.77 (m, 1H, H_6), 7.69 (d, J = 6.0 Hz, 2H, H_4, H_7), 7.66–7.64 (m, 1H, H_5), 7.41–7.36 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$), 2.45 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8, 150.4, 141.4, 139.8, 137.7, 134.0, 130.5, 125.6, 124.9, 122.6, 120.6, 120.1, 111.0, 21.2. HRMS ((+)ESI): *m*/*z* Calcd for $C_{16}H_{12}N_4O$ + Na: 299.0903, found 299.0886.

2-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5b). White solid. mp 181–183°C. IR (KBr) (ν_{max}, cm^{-1}): 3095 (C—H, Ar), 1644 (C═N), 1589, 1473, 1450 (C═C), 1401 (C—N), 1233 (C—O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H, triazole), 7.84–7.81 (m, 2H, H_5, H_6), 7.81–7.78 (m, 1H, $H_{2'}$)7.68–7.63 (m, 1H, $H_{6'}$), 7.59 (t, J = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.52 (t, J = 6.0 Hz, 1H, $H_{4'}$), 7.44–7.37 (m, 2H, H_4, H_7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 150.4, 141.4, 137.9, 136.4, 130.0, 129.5, 125.7, 125.0, 122.6, 120.7, 120.2, 111.0. HRMS ((+)ESI): *m*/*z* Calcd for $C_{15}H_{10}N_4O$ + Na: 285.0747, found 285.0732.

2-(1-(2-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5c). Light yellow solid. mp 179–181°C. IR (KBr) (ν_{max}, cm^{-1}): 3090 (C—H, Ar), 1638 (C═N), 1510, 1495, 1454 (C═C), 1400 (C—N), 1240 (C—O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, 1H, triazole),

7.82–7.76 (m, 1H, H_5), 7.68–7.63 (m, 1H, H_6), 7.50–7.37 (m, 6H, H_4, H_7, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 2.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8, 150.4, 141.4, 137.2, 135.7, 133.6, 131.7, 130.5, 127.1, 126.1, 125.9, 125.7, 124.9, 120.1, 111.0, 17.9. HRMS ((+)ESI): *m*/*z* Calcd for $C_{16}H_{12}N_4O$ + Na: 299.0903, found 299.0875.

2-(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5d). White solid. mp 167–168°C. IR (KBr) (ν_{max}, cm^{-1}): 3107 (C─H, Ar), 1645 (C═N), 1590, 1495, 1451 (C═C), 1395 (C─N), 1245 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H, triazole), 7.89 (t, J = 1.9 Hz, 1H, $H_{6'}$), 7.81–7.77 (m, 1H, H_5), 7.73 (dt, J = 7.7, 1.8 Hz, 1H, H_6), 7.67–7.62 (m, 1H, $H_{2'}$), 7.55–7.47 (m, 2H, H_4, H_7), 7.44–7.37 (m, 2H, $H_{3'}$, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 150.3, 141.3, 138.1, 137.1, 135.8, 131.1, 129.6, 125.8, 125.0, 122.5, 121.0, 120.2, 118.6, 111.0. HRMS ((+)ESI): *m*/*z* Calcd for $C_{15}H_9ClN_4O$ + Na: 319.0357, found 319.0328.

2-(1-(2-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5e). White solid. mp 176–177°C. IR (KBr) (ν_{max}, cm^{-1}): 3123 (C─H, Ar), 1635 (C═N), 1506, 1475, 1451 (C═C), 1400 (C─N), 1240 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (s, 1H, triazole), 8.08 (t, J = 7.0 Hz, 1H, $H_{2'}$), 7.84–7.78 (m, 1H, H_5), 7.68–7.63 (m, 1H, H_6), 7.54–7.48 (m, 1H, H_7), 7.43–7.34 (m, 4H, H_4, $H_{3'}$, $H_{4'}$, $H_{5'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.5, 154.5, 152.0, 150.4, 141.4, 137.7, 131.0 (d, J = 8.0 Hz, CH), 125.7, 125.6, 125.5 (d, J = 4.0 Hz, CH), 125.0, 124.8, 120.2, 117.2 (d, J = 20.0 Hz, CH), 111.0. HRMS ((+)ESI): *m*/*z* Calcd for $C_{15}H_9FN_4O$ + Na: 303.0653, found 303.0632.

6-Methyl-2-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5f). Brick red solid. mp 214–215°C. IR (KBr) (ν_{max}, cm^{-1}): 3121 (C─H, Ar), 1637 (C═N), 1522, 1510 (C═C), 1401 (C─N), 1244 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (s, 1H, triazole), 7.69 (d, J = 4.0 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.64 (d, J = 8.0 Hz, 1H, H_5), 7.44 (s, 1H, H_7), 7.36 (d, J = 8.1 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.20 (d, J = 8.9 Hz, 1H, H_4), 2.51 (s, 3H, 6-CH_3), 2.44 (s, 3H, H_5, 4′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 150.7, 139.7, 139.24, 137.9, 136.2, 134.1, 130.4, 126.2, 122.3, 120.6, 119.4, 111.1, 21.8, 21.1. HRMS ((+)ESI).: *m*/*z* Calcd for $C_{17}H_{14}N_4O$ + Na: 313.1060, found 313.1030.

5-Chloro-2-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5g). White solid. mp 184–185°C. IR (KBr) (ν_{max}, cm^{-1}): 3120 (C─H, Ar), 1636 (C═N), 1519, 1507, 1449 (C═C), 1400 (C─N), 1255 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (s, 1H, triazole), 7.76 (d, J = 1.9 Hz, 1H, H_4), 7.69 (d, J = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.57 (d, J = 8.7 Hz, 1H, H_7), 7.39–7.36 (m, 3H, H_6, $H_{3'}$, $H_{5'}$), 2.46 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1, 149.0, 142.6, 139.9, 137.3, 134.0, 130.5, 125.9, 122.9, 120.6, 120.1, 111.7, 21.2. HRMS ((+)ESI): *m*/*z* Calcd for $C_{16}H_{11}ClN_4O$ + Na: 333.0514, found 333.0530.

2-(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-6-methylbenzo[*d*]oxazole (5h). White solid. mp 172–173°C. IR (KBr) (ν_{max}, cm^{-1}): 3116 (C─H, Ar), 1639 (C═N), 1510, 1486, 1464 (C═C), 1402 (C─N), 1252 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (s, 1H, triazole), 7.89 (t, J = 1.9 Hz, 1H, $H_{6'}$), 7.72 (dt, J = 7.7, 1.8 Hz, 1H, $H_{2'}$), 7.65 (d, J = 8.1 Hz, 1H, H_5), 7.55–7.47 (m, 2H, H_7, $H_{4'}$), 7.44 (s, 1H, $H_{3'}$), 7.21 (d, J = 7.3 Hz, 1H, H_4), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.9, 150.7, 139.2, 138.3, 137.2, 136.4, 135.9, 131.1, 129.5, 126.3, 122.2, 121.0, 119.5, 118.6, 111.1, 21.8. HRMS ((+)ESI): *m*/*z* Calcd for $C_{16}H_{11}ClN_4O$ + Na: 333.0514, found 333.0524.

2-(1-(2-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)-6-methylbenzo[*d*]oxazole (5i). Light pink solid. mp 190–191°C. IR (KBr) (ν_{max}, cm^{-1}): 3176 (C─H, Ar), 1634 (C═N), 1519, 1508, 1475 (C═C), 1400 (C─N), 1254 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, J = 2.6 Hz, 1H, triazole), 8.07 (t, J = 8.0 Hz, 1H, $H_{2'}$), 7.66 (d, J = 8.1 Hz, 1H, H_5), 7.53–7.48 (m, 1H, H_7), 7.45 (s, 1H, $H_{3'}$), 7.40–7.33 (m, 2H, $H_{4'}$, $H_{5'}$), 7.21 (d, J = 8.1 Hz, 1H, H_4), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.0, 154.5, 152.1, 150.7, 139.2, 137.9, 136.3, 130.9 (d, J = 8 Hz, CH), 126.2, 125.4 (d, J = 4 Hz, CH), 125.4, 124.9, 119.5, 117.2 (d, J = 19 Hz, CH), 111.1, 21.8. HRMS ((+)ESI): *m*/*z* Calcd for $C_{16}H_{11}FN_4O$ + Na: 317.0809, found 317.0818.

5-Chloro-2-(1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5j). Light red solid. mp 205–206°C. IR (KBr) (ν_{max}, cm^{-1}): 3097 (C─H, Ar), 1634 (C═N), 1506, 1474, 1448 (C═C), 1400 (C─N), 1259 (C─O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83 (d, J = 2.5 Hz, 1H, triazole), 8.08 (t, J = 7.9 Hz, 1H, H_4), 7.77 (d, J = 1.9 Hz, 1H, H_7), 7.57 (d, J = 8.6 Hz, 1H, $H_{2'}$), 7.55–7.49 (m, 1H, H_6), 7.41–7.34 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 154.5, 152.0, 149.0, 142.6, 137.3, 131.1 (d, J = 8 Hz, CH), 130.5, 126.0, 125.9, 125.5 (d, J = 4 Hz, CH), 124.8, 120.2, 117.3(d, J = 20 Hz, CH), 111.7. HRMS ((+)

ESI): *m/z* Calcd for $C_{15}H_8FClN_4O$ + Na: 337.0263, found 337.0257.

5-Chloro-2-(1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5k). Off-white solid. mp 205–206°C. IR (KBr) (ν_{max}, cm^{-1}): 3099 (C—H, Ar), 1592 (C═N), 1584, 1490, 1448 (C═C), 1403 (C—N), 1257 (C—O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H, triazole), 7.90 (t, J = 1.8 Hz, 1H, $H_{6'}$), 7.77 (d, J = 2.0 Hz, 1H, H_4), 7.72 (dt, J = 7.6, 1.9 Hz, 1H, H_7), 7.59–7.51 (m, 3H, $H_{2'}$, $H_{3'}$, $H_{4'}$), 7.38 (dd, J = 8.7, 2.1 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 149.0, 142.5, 137.7, 137.1, 136.0, 131.1, 130.8, 129.7, 126.1, 122.8, 121.1, 120.2, 118.6, 111.7. HRMS ((+)ESI): *m/z* Calcd for $C_{15}H_8Cl_2N_4O$ + Na: 352.9967, found 352.9950.

Methyl 4-(4-((6-methylbenzo[*d*]oxazol-2-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzoate (5l). Light yellow solid. mp 197–198°C. IR (KBr) (ν_{max}, cm^{-1}): 3093 (C—H, Ar), 1723 (C═O), 1644 (C═N), 1615, 1485, 1437 (C═C), 1378 (C—N), 1249 (C—O). ^1H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H, triazole), 7.98 (d, J = 8.2 Hz, 2H, Ar—H), 7.67 (d, J = 8.1 Hz, 1H, Ar—H), 7.62 (s, 1H, Ar—H), 7.50 (d, J = 8.2 Hz, 2H, H_5, H_7), 7.24 (d, J = 8.1 Hz, 1H, H_4), 5.85 (s, 2H, CH_2), 3.85 (s, 3H, 6-CH_3), 2.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.8, 155.3, 149.9, 140.6, 138.8, 136.1, 135.7, 129.6, 129.4, 128.2, 127.0, 126.1, 119.12, 110.9, 52.7, 52.2, 21.2. HRMS ((+)ESI): *m/z* Calcd for $C_{19}H_{16}N_4O_3$ + Na: 371.1115, found 371.1105.

6-Methyl-2-(1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5m). Off-white solid. mp 184–186°C. IR (KBr) (ν_{max}, cm^{-1}): 3088 (C—H, Ar), 1635 (C═N), 1510, 1497, 1467 (C═C), 1400 (C—N), 1240 (C—O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.45 (s, 1H, triazole), 7.65 (d, J = 8.1 Hz, 1H, $H_{4'}$), 7.50–0.37 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{5'}$, H_5, H_7), 7.21 (d, J = 8.1 Hz, 1H, H_4), 2.53 (s, 3H, 6-CH_3), 2.29 (s, 3H, 6′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 150.7, 139.3, 137.4, 136.2, 135.8, 133.6, 131.7, 130.4, 127.1, 126.2, 126.0, 125.9, 119.4, 111.1, 21.8, 17.9. HRMS ((+)ESI): *m/z* Calcd for $C_{17}H_{14}Cl_2N_4O$ + Na: 313.1060, found 313.1066.

7-Chloro-2-(1-(2-methylphenyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5n). White solid. mp 138–140°C. IR (KBr) (ν_{max}, cm^{-1}): 3072 (C—H, Ar), 1651 (C═N), 1503, 1466, 1446 (C═C), 1380 (C—N), 1256 (C—O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (s, 1H, triazole), 7.76 (d, J = 2.0 Hz, 1H, H_4), 7.57 (d, J = 8.7 Hz, 1H, H_7), 7.50–7.36 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, H_6), 2.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1, 149.0, 142.6, 136.8, 135.7, 133.6, 131.7, 130.5, 130.5, 127.1, 126.4, 126.0, 125.9, 120.1, 111.7, 17.9. HRMS ((+)ESI): *m/z* Calcd for $C_{16}H_{11}ClN_4O$ + Na: 333.0514, found 333.0513.

6-Methyl-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5o). Brick red solid. mp 199–200°C. IR (KBr) (ν_{max}, cm^{-1}): 3051 (C—H, Ar), 1635 (C═N), 1515, 1502, 1482 (C═C), 1400 (C—N), 1343 (C—O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (s, 1H, triazole), 7.82 (d, J = 8.1 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.65 (d, J = 8.1 Hz, 1H, $H_{3'}$), 7.58 (t, J = 7.6 Hz, 2H, $H_{4'}$, $H_{5'}$), 7.51 (m, J = 8.0 Hz, 1H, H_5), 7.44 (s, 1H, H_7), 7.20 (d, J = 8.8 Hz, 1H, H_4), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 150.7, 139.2, 138.0, 136.4, 136.3, 130.0, 129.5, 126.2, 122.4, 120.7, 119.5, 111.1, 21.8. HRMS ((+)ESI): *m/z* Calcd for $C_{16}H_{12}N_4O$ + Na: 299.0903, found 299.0917.

5-Chloro-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)benzo[*d*]oxazole (5p). Orange solid. mp 203–205°C. IR (KBr) (ν_{max}, cm^{-1}): 3135 (C—H, Ar), 1634 (C═N), 1505, 1450, 1428 (C═C), 1400 (C—N), 1261 (C—O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H, triazole), 7.83–7.80 (m, 2H, H_4, H_7), 7.76 (d, J = 2.0 Hz, 1H, $H_{2'}$), 7.61–7.50 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.37 (dd, J = 8.7, 2.1 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 149.0, 142.6, 137.5, 136.3, 130.5, 130.0, 129.6, 126.0, 122.9, 120.7, 120.1, 111.7. HRMS ((+)ESI): *m/z* Calcd for $C_{15}H_9ClN_4O$ + Na: 319.0357, found 319.0358.

Methyl 4-((4-(benzo[*d*]oxazol-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)benzoate (5q). Light yellow solid. mp 192–194°C. IR (KBr) (ν_{max}, cm^{-1}): 3098 (C—H, Ar), 1712 (C═O), 1645 (C═N), 1615, 1445, 1433 (C═C), 1282 (C—N), 1240 (C—O). ^1H NMR (400 MHz, DMSO-d_6) δ: 9.19 (s, 1H, triazole), 7.98 (d, J = 8.2 Hz, 2H, Ar—H), 7.83–7.80 (m, 2H, H_5, H_6), 7.51 (d, J = 8.2 Hz, 2H, H_4, H_7), 7.47–7.41 (m, 2H, Ar—H), 5.86 (s, 2H, CH_2), 3.84 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.8, 155.8, 149.6, 141.0, 140.6, 136.0, 129.6, 129.4, 128.2, 127.3, 125.6, 125.0, 119.8, 111.0, 152.7, 152.2. HRMS ((+)ESI): *m/z* Calcd for $C_{18}H_{14}N_4O_3$ + Na: 357.0958, found 357.0955.

Antifungal activity

The antifungal activity of the target compounds against BC and FV was evaluated at the College of Life Science, Henan Normal University, using hymexazol as positive control. The procedures were as follows[22]:

A stock solution of each compound was prepared at 1.0 mg/mL using DMSO as solvent. A working solution (0.04 mg/mL) was then prepared by diluting the stock solution (0.04 mL) into a 10-cm-diameter Petri dish containing potato dextrose agar (PDA, 10 mL). Before the plate solidification, the PDA was completely mixed by turning around the Petri dish in the sterilized operation disk six times to decentralize the compounds in PDA evenly. Then 0.8 mm of diameter of the fungi cake was vaccinated on the plate and cultured in an incubator at 28°C. At the same time, blank control and positive control were prepared using the same procedures. After 48 h, the diameter of fungi spread was measured. The antifungal activity was evaluated using the antifungal inhibition ratio, which was calculated by comparing the average diameter of fungi spread with that of the corresponding control, according to Eq. (1).

$$W = \frac{A - B}{A} \times 100 \quad (1)$$

where W is the antifungal inhibition ratio (*in vivo*) (%), A is the average diameter of the blank fungi spread *in vivo*, and B is the average diameter of drug-containing fungi spread *in vivo*.

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Supporting information

Additional supporting information is available in the online version of this article.

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