Li Wan, Yang Zihui, Hu Aixi*, Ye Jiao, Ou Xiaoming, Pei Hui, He Lian and Li Jianming

Synthesis and fungicidal activities of 2-{[(2-(1*H*-1,2,4-triazol-1-yl)-ethylidene)amino] oxy}alkanamides containing dihydrobenzofuran

https://doi.org/10.1515/hc-2017-0245
Received November 29, 2017; accepted April 16, 2018; previously published online November 13, 2018

Abstract: In order to find new compounds with high fungicidal activity, acetamide derivatives **4a–x** were rationally designed, synthesized, characterized and tested against various fungi *in vivo*. The bioassay results indicate that compounds **4k,m,o,r** exhibit an 80% inhibition rate against *Rhizoctonia solani* at 500 mg/L, and compound **4j** shows an 80% inhibition rate against *Blumeria graminis* at 500 mg/L. Therefore, compounds of **4** are promising fungicidal candidates worthy of further development.

Keywords: amides; dihydrobenzofuran; fungicidal activity; synthesis.

Introduction

Dihydrobenzofuran moieties are widely distributed in natural products [1, 2]. Recently, novel dihydrobenzofuran derivatives have been designed and synthesized as antitumor, insecticidal, herbicidal and fungicidal agents [3–12]. In order to develop new fungicides, our group has synthesized compounds **A** [13] and **B** [14] with potent fungicidal activity (Figure 1). In the present report, their analogues **4a–x** (Scheme 1) were synthesized and screened for fungicidal activity *in vivo*.

***Corresponding author: Hu Aixi,** College of Chemistry and Chemical Engineering, Hunan University, Changsha, China, e-mail: axhu@hnu.edu.cn
Li Wan: College of Chemistry and Chemical Engineering, Hunan University, Changsha, China; and College of Pharmaceutical Sciences, Hebei University, Baoding, China
Yang Zihui and Ye Jiao: College of Chemistry and Chemical Engineering, Hunan University, Changsha, China
Ou Xiaoming, Pei Hui, He Lian and Li Jianming: Hunan Research Institute of Chemical Industry, Changsha, China

Results and discussion

The synthetic route to compounds of **4** is outlined in Scheme 1. The intermediate products **2** were prepared as previously described [5, 15]. Compounds of **3** were obtained by treatment of compounds of **2** with hydroxylamine hydrochloride. Subsequently, compounds of **4** were prepared by the reaction of **3** with 2-chloroacetamides (R^3 = H) or 2-chloropropionamides (R^3 = Me) using the Williamson etherification catalyzed by TBAB, KI and NaOH in toluene. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis or high-resolution mass spectrometry (HRMS). The crystal structure of the intermediate product **3a** was determined by single crystal X-ray diffraction. The single crystal X-ray analysis of compound **3a** shows the orthorhombic crystal and the space group $P2_12_12_1$ with each crystal unit made up of four molecules. The CCDC number is 1500344. As can be seen from Figure 2, the configuration of the double bond (C11=N1) is *Z* [13, 16]. The distance and angle are 2.68 Å and 171.0°, respectively. The intermolecular hydrogen bond appears to play an important role in stabilizing the crystal structure (Figure 3).

The preliminary bioassay results indicate that some of compounds **4** show potent activities against the selected fungi *Rhizoctonia solani* and *Blumeria graminis* (*B. graminis*) that are better than the activities of the lead compounds **A** and **B** at 500 mg/L [13, 14]. For instance, compound **4k** with the inhibitory activity of 80%, **4m** (80%), **4o** (80%) and **4r** (80%) are the most potent agents. Compounds **4d** (60%), **4e** (60%) and **4f** (70%) also show better fungicidal activities than the commercial fungicide azoxystrobin (50%). Compounds **4t**, **4v** and **4x** display a 30% inhibitory activity. Analysis of the structure-activity relationships (SARs) shows that compounds of **4** substituted with an alkoxy group (R^1 = OMe, OEt or OPr-*n*) are highly active against *B. graminis* at the concentration of 500 mg/L. Compound **4j** shows the best inhibitory activity of 80%, followed by **4g** (78%) and **4i** (70%). Comparison of the activities of acetamides (R^3 = H, **4a–t**) with the

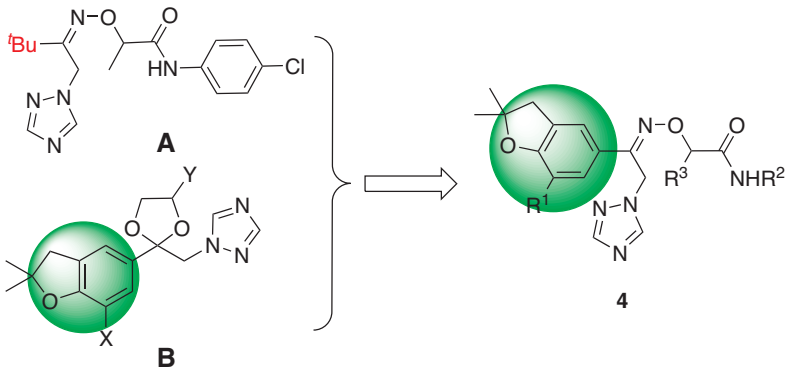
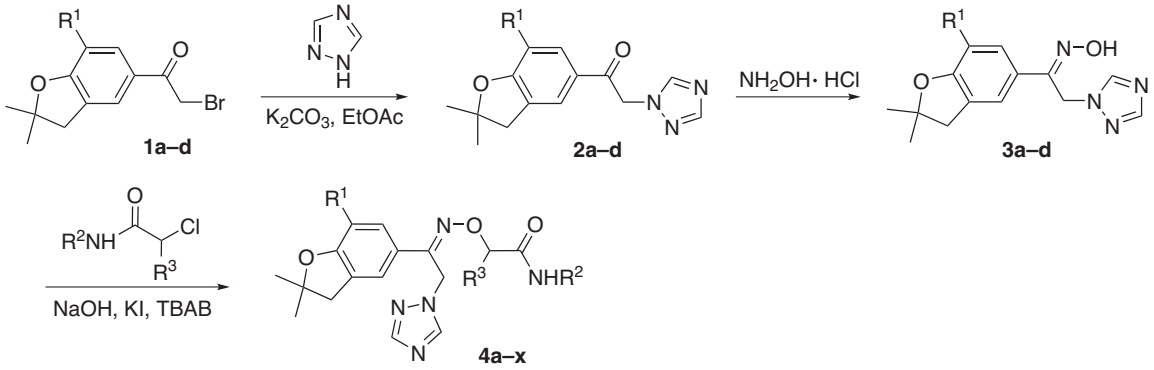


Figure 1 Structures of compounds **A** and **B** synthesized previously. Compounds of **4** were synthesized as part of this work.



1–3a: R^1 = H
1–3b: R^1 = OMe
1–3c: R^1 = OEt
1–3d: R^1= O^{n}Pr

4a: R^1 = H; R^2 = ^{c}Pr; R^3 = H
4b: R^1 = H; R^2 = Ph; R^3 = H
4c: R^1 = H; R^2 = 2,6-$(CH_3)_2C_6H_3$; R^3 = H
4d: R^1 = H; R^2 = 4-FC_6H_4; R_3 = H
4e: R^1 = H; R^2 = 4-ClC_6H_4; R_3 = H
4f: R^1 = H; R^2 = $CH_2C_6H_5$; R_3 = H
4g: R^1 = OMe; R^2 = 2,6-$(CH_3)_2C_6H_3$; R^3 = H
4h: R^1 = OMe; R^2 = 4-FC_6H_4; R^3 = H
4i: R^1 = OMe; R^2 = $CH_2C_6H_5$; R^3 = H
4j: R^1 = OEt; R^2 = ^{c}Pr; R^3 = H
4k: R^1 = OEt; R^2 = 2,6-$(CH_3)_2C_6H_3$; R^3 = H
4l: R^1 = OEt; R^2 = 4-FC_6H_4; R^3 = H

4m: R^1 = OEt; R^2 = 4-ClC_6H_4; R^3 = H
4n: R^1 = OEt; R^2 = $CH_2C_6H_5$; R^3 = H
4o: R^1 = O^{n}Pr; R^2 = ^{c}Pr; R^3 = H
4p: R^1 = O^{n}Pr; R^2 = Ph; R^3 = H
4q: R^1 = O^{n}Pr; R^2 = 4-FC_6H_4; R^3 = H
4r: R^1 = O^{n}Pr; R^2 = 4-ClC_6H_4; R^3 = H
4s: R^1 = O^{n}Pr; R^2 = $CH_2C_6H_5$; R^3 = H
4t: R^1 = OMe, R^2 = 2-C_5H_4N; R^3 = H
4u: R^1 = OMe; R^2 = Ph; R^3 = Me
4v: R^1 = OMe; R^2 = 2,6-$(CH_3)_2C_6H_3$; R^3 = Me
4w: R^1 = OMe; R^2 = 4-ClC_6H_4; R^3 = Me
4x: R^1 = OMe; R^2 = 2-C_5H_4N; R^3 = Me

Scheme 1 Synthetic route to target compounds **4a–x**.

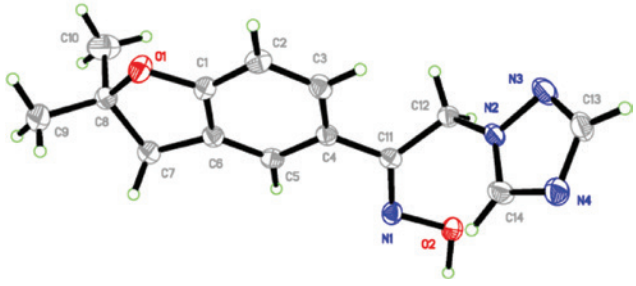


Figure 2 Crystal structure of compound **3a**.

activities of propanamides (R^3 = Me, **4u–x**) reveals that the acetamides possess better antifungal activity.

Conclusion

Twenty-four compounds **4a–x** were synthesized and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, elemental analysis, HRMS and X-ray diffraction analysis.

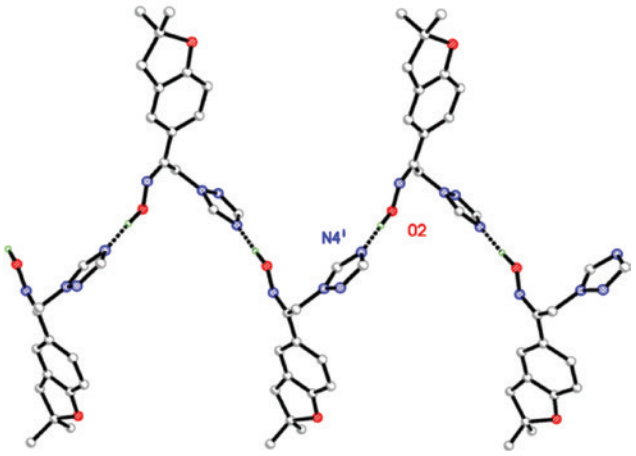


Figure 3 Hydrogen bonds for compound **3a**.

Compounds **4k**, **4m**, **4o** and **4r** show good antifungal activities against *R. solani*, and compounds **4g** and **4j** are highly active against *B. graminis*.

Experimental

All reagents were of analytical grade. Melting points were measured on an X-4 electrothermal digital melting point apparatus and are uncorrected. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60GF-254) and compounds were visualized with UV light. Flash chromatography was performed using silica gel (200–400 mesh) eluting with a mixture of petroleum ether and ethyl acetate. ^{1}HNMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker AV-400 spectrometer with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed on a Vario EL III instrument. The X-ray intensity data were collected on a Bruker AXS SMART 1000 CCD diffractometer. The preparations of compounds **2a–d** have been previously reported [5, 15].

General procedure for synthesis of compounds 3a–d

A mixture of **2** (12.2 mmol), $NH_2OH \cdot HCl$ (18.2 mmol) and CH_3COONa (18.2 mmol) in EtOH (50 mL) was heated under reflux. The progress of the reaction was monitored by TLC. The mixture was cooled and filtered, and the filtrate was concentrated. The resultant precipitate of **3** was crystallized from a mixture of ethanol and water.

(*Z*)-1-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone oxime (3a) White solid; yield 78%; mp 149–151°C; ^{1}H NMR: δ 1.46 (s, 6H), 2.99 (s, 2H), 5.43 (s, 2H), 6.72 (d, 1H, J = 8 Hz), 7.52 (d, 1H, J = 8 Hz), 7.54 (s, 1H), 7.97 (s, 1H), 8.35 (s, 1H); ^{13}C NMR: δ 28.1, 42.5, 43.6, 87.8, 109.6, 123.3, 125.8, 127.1, 128.1, 144.3, 150.9, 151.6, 160.4. Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.67; H, 5.94, N, 20.62.

(*Z*)-1-(7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone oxime (3b) White solid; yield 94%; mp 203–206°C; ^{1}H NMR: δ 1.52 (s, 6H), 3.04 (s, 2H), 3.88 (s, 3H), 5.44 (s, 2H), 7.20 (s, 1H), 7.26 (s, 1H), 7.96 (s, 1H), 8.35 (s, 1H). Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 60.02; H, 6.02; N, 18.57.

(*Z*)-1-(7-Ethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone oxime (3c) White solid; yield 77.4%; mp 181–184°C; ^{1}H NMR: δ 1.42 (t, 3H, J = 8 Hz), 1.51 (s, 6H), 3.02 (s, 2H), 4.12 (q, 2H, J = 8 Hz), 5.43 (s, 2H), 7.17 (s, 1H), 7.22 (s, 1H), 7.96 (s, 1H), 8.34 (s, 1H). Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 61.00; H, 6.34; N, 17.75.

(*Z*)-1-(2,2-Dimethyl-7-propoxy-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone oxime (3d) White solid; yield 78%; mp 161–163°C; ^{1}H NMR: δ 0.98 (t, 3H, J = 7 Hz), 1.50 (s, 6H), 1.78 (q, 2H, J = 7 Hz), 2.98 (s, 2H), 4.02 (t, 2H, J = 7 Hz), 5.48 (s, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.97 (s, 1H), 8.32 (s, 1H). Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61.77; H, 6.28; N, 12.99. Found: C, 61.67; H, 6.25; N, 12.95.

General synthetic procedure for compounds 4a–x

A mixture of **3** (0.8 mmol), *N*-substituted-2-chloroacetamide or *N*-substituted-2-chloropropionamide (1 mmol), TBAB (0.4 mmol) and KI (0.8 mmol) in toluene (10 mL) was treated dropwise at room temperature with 30% NaOH (1.13 g) and then stirred at 60°C for 3 h. The mixture was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography to give **4a–x**.

***N*-Cyclopropyl-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4a)** Yellow solid; yield 59%; mp 142–144°C; ^{1}H NMR: δ 0.56 (m, 2H), 0.75–0.85 (m, 2H), 1.47 (s, 6H), 2.75–2.79 (m, 1H), 3.01 (s, 2H), 4.74 (s, 2H), 5.41 (s, 2H), 6.72 (d, 1H, J = 8 Hz), 7.35 (d, 1H, J = 8 Hz), 7.42 (s, 1H), 7.46 (s, 1H), 7.97 (s, 1H), 8.20 (d, 1H, J = 4 Hz); ^{13}C NMR: δ 6.1, 22.0, 28.1, 42.4, 43.0, 73.8, 88.1, 109.6, 123.4, 124.2, 126.7, 128.6, 143.7, 151.8, 152.2, 161.1, 170.9. Anal. Calcd for $C_{19}H_{22}N_5O_3$: C, 61.77; H, 6.28; N, 12.99. Found: C, 61.67; H, 6.20; N, 12.90.

***N*-Phenyl-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-ylethylideneaminooxy]acetamide (4b)** White solid; yield 49.3%; mp 46–48°C; ^{1}H NMR: δ 1.50 (s, 6H), 3.03 (s, 2H), 4.73 (s, 2H), 5.23 (s, 2H), 6.78 (d, 1H, J = 8 Hz), 7.14 (m, 2H), 7.39 (m, 5H), 7.90 (s, 1H), 8.07 (s, 1H); ^{13}C NMR: δ 28.4, 42.5, 43.0, 73.9, 88.2, 109.4, 123.6, 124.3, 125.7, 126.8, 127.5, 127.6, 127.9, 128.6, 128.8, 138.2, 143.7, 152.0, 152.2, 161.1, 169.6. Anal. Calcd for $C_{22}H_{23}N_5O_3$: C, 65.17; H, 5.72; N, 11.84. Found: C, 65.07; H, 5.63; N, 11.74.

***N*-(2,6-Dimethylphenyl)-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4c)** Brown solid; yield 45%; mp 74–76°C; ^{1}H NMR: δ 1.47 (s, 6H), 2.18 (s, 6H), 3.10 (s, 2H), 4.94, 4.95 (2s, 2H), 5.43 and 5.49 (2s, 2H), 7.20 (m, 3H), 7.35 (m, 3H), 8.17 (s, 1H), 8.62 (s, 1H), 9.00 (s, 1H); ^{13}C NMR: δ 18.4, 28.1, 42.4, 74.2, 88.6, 109.8, 123.4, 124.1, 126.8, 127.4, 128.2, 128.3, 128.6, 129.6, 133.4, 135.7, 136.0, 143.9, 152.1, 161.0, 161.4, 168.3. Anal. Calcd for $C_{24}H_{27}N_5O_3$: C, 66.49; H, 6.28; N, 16.16. Found: C, 66.39; H, 6.20; N, 16.10.

***N*-(4-Fluorophenyl)-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4d)** Brown solid; yield 55%; mp 61–63°C; ^{1}H NMR: δ 1.28 (s, 6H),

2.82 (s, 2H), 4.72 (s, 2H), 5.41 (s, 2H), 6.53 (d, 1H, J = 8 Hz), 6.86 (t, 2H, $J_{H\text{-}F}$ = 8 Hz), 7.27 (d, 1H, J = 8 Hz), 7.38 (m, 3H), 7.70 (s, 1H), 8.35 (s, 1H), 9.43 (s, 1H); ^{13}C NMR: δ 28.1, 42.4, 73.9, 88.3, 109.8, 115.5, 115.7, 116.4, 116.6, 122.8, 123.6, 124. 1, 126.8, 128.8, 133.3, 144.0, 152.3, 152.6, 160.9, 161.4, 167.9. Anal. Calcd for $C_{22}H_{22}FN_5O_3$: C, 62.40; H, 5.24; N, 16.54. Found: C, 62.30; H, 5.14; N, 16.46.

***N*-(4-Chlorophenyl)-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4e)** Yellow solid; yield 40%; mp 57–59°C; ^{1}H NMR: δ 1.46 (s, 6H), 2.99 (s, 2H), 4.88 (s, 2H), 5.49 (s, 2H), 6.72 (d, 1H, J = 8.0 Hz), 7.27 (m, 2H), 7.38 (m, 2H), 7.55 (d, 2H, J = 8 Hz), 7.91 (s, 1H), 8.26 (s, 1H), 9.20 (s, 1H); ^{13}C NMR: δ 28.1, 43.0, 73.8, 88.3, 109.8, 121.1, 122.3, 123.5, 124.2, 124.7, 125.7, 126.9, 128.8, 128.9, 129.1, 129.7, 136.1, 152.3, 155.5, 161.4, 167.9. Anal. Calcd for $C_{22}H_{22}ClN_5O_3$: C, 60.07; H, 5.04; N, 15.92. Found: C, 59.90; H, 4.92; N, 15.82.

***N*-Benzyl-2-[1-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylidene aminooxy]acetamide (4f)** Yellow solid; yield 65%; mp 78–80°C; ^{1}H NMR: δ 1.47 (s, 6H), 2.99 (s, 2H), 4.54 (d, 2H, J = 6 Hz), 4.83 (s, 2H), 5.39 (s, 2H), 6.69 (d, 1H, J = 8 Hz), 7.22 (d, 1H, J = 8 Hz), 7.28 (m, 5H), 7.42 (s, 1H), 8.04 (s, 1H), 8.11 (s, 1H); ^{13}C NMR: δ 27.9, 42.2, 42.7, 73.5, 76.7, 87.9, 109.4, 123.3, 124.1, 126.6, 127.2, 127.6, 128.3, 137.9, 143.6, 151.8, 160.8, 169.5. Anal. Calcd for $C_{23}H_{25}N_5O_3$: C, 65.85; H, 6.01; N, 11.94. Found: C, 65.80; H, 5.93; N, 11.87.

***N*-(2,6-Dimethylphenyl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4g)** Yellow solid; yield 47%; mp 55–57°C; ^{1}H NMR: δ 1.52 (s, 6H), 2.20 (s, 6H), 3.03 (s, 2H), 3.86 (s, 3H), 4.95 (s, 2H), 5.48 (s, 2H), 7.05 (m, 3H), 7.17 (s, 1H), 7.54 (s, 1H), 8.18 (s, 1H), 8.92 (s, 1H); ^{13}C NMR: δ 18.4, 28.2, 42.8, 43.0, 55.9, 73.8, 76.8, 77.0, 77.25, 88.9, 109.1, 115.9, 124.7, 127.4, 128.1, 128.3, 133.3, 135.6, 143.8, 144.9, 149.9, 152.2, 152.2, 168.2. Anal. Calcd for $C_{25}H_{29}N_5O_4$: C, 64.78; H, 6.31; N, 15.11. Found: C, 64.68; H, 6.23; N, 15.01. HRMS. Calcd for $C_{25}H_{30}N_5O_4$, $(M+H)^+$: m/z 464.2220. Found: m/z 464.2289.

***N*-(4-Fluorophenyl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4h)** Gray solid; yield 32%; mp 73–75°C; ^{1}H NMR: δ 1.51 (s, 6H), 3.02 (s, 2H), 3.86 (s, 3H), 4.89 (s, 2H), 5.48 (s, 2H), 7.01 (s, 1H), 7.03 (s, 1H), 7.07 (m, 2H), 7.50–7.57 (m, 2H), 7.91 (s, 1H), 8.26 (s, 1H), 9.11 (s, 1H); ^{13}C NMR: δ 27.8, 42.6, 43.0, 55.7, 73.6, 88.7, 108.9, 115.7, 120.6, 124.4, 128.2, 128.6, 137.0, 143.5, 144.1, 144.7, 149.5, 152.0, 152.2, 154.4, 166.1, 167.4. Anal. Calcd for $C_{23}H_{24}FN_5O_4$: C, 60.92; H, 5.33; N, 15.44. Found: C, 60.83; H, 5.23; N, 15.34.

***N*-Benzyl-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4i)** Yellow solid; yield 59%; mp 143–145°C; ^{1}H NMR: δ 1.52 (s, 6H), 3.02 (s, 2H), 3.86 (s, 3H), 4.55 (s, 2H), 5.39 (s, 2H,), 6.93 (s, 1H), 7.07 (s, 1H), 7.28 (m, 5H), 8.00 (s, 1H), 8.11 (s, 1H); ^{13}C NMR: δ 28.1, 42.5, 43.1, 55.8, 55.9, 74.3, 89.2, 109.1, 116.0, 124.9, 127.5, 128.4, 128.6, 138.2, 143.6, 144.8, 149.8, 151.8, 152.1, 153.6, 163.1, 169.6. Anal. Calcd for $C_{24}H_{27}N_5O_4$: C, 64.13; H, 6.05; N, 15.58. Found: C, 64.03; H, 5.96; N, 15.48.

***N*-Cyclopropyl-2-[1-(7-ethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4j)** Gray solid; yield 35%; mp 80–82°C; ^{1}H NMR: δ 0.57 (t, 2H, J = 4 Hz), 0.79 (t, 2H, J = 7 Hz), 1.02 (t, 3H, J = 7 Hz), 1.51 (s, 6H), 2.77–2 (m, 1H), 3.02 (s, 3H), 4.12 (q, 2H, J = 7 Hz), 4.75 (d, 2H, J = 4 Hz), 5.45 (s, 2H), 7.03 (s, 1H), 7.08 (s, 1H), 7.99 (s, 1H), 8.33 (s, 1H); ^{13}C NMR: δ 6.5, 13.7, 22.0, 24.3, 28.4, 43.1, 43.2, 64.9, 73.9, 88.4, 111.1, 115.8, 124.8, 129.1, 136.4, 144.0, 150.2, 152.6, 162.0, 171.1. Anal. Calcd for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58; N, 16.94. Found: C, 60.93; H, 6.50; N, 16.84.

***N*-(2,6-Dimethylphenyl)-2-[1-(7-ethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4k)** Brown solid; yield 35%; mp 83–85°C; ^{1}H NMR: δ 1.42 (t, 3H, J = 7 Hz), 1.52 (s, 6H), 2.20 (m, 6H), 3.01 (d, 2H, J = 3.5 Hz), 4.09 (t, 2H, J = 7 Hz), 4.81 (s, 1H), 4.96 (s, 1H), 5.51 (s, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.12–7.20 (m, 3H), 8.23 (s, 1H), 8.58 (s, 1H), 8.88 (s, 1H); ^{13}C NMR: δ 14.6, 18.3, 28.1, 42.5, 42.9, 64.5, 73.6, 88.6, 110.5, 110.6, 115.7, 124.4, 127.3, 128.0, 128.5, 133.2, 135.5, 143.9, 150.0, 151.9, 152.1, 168.3. Anal. Calcd for $C_{26}H_{31}N_5O_4$: C, 65.39; H, 6.54; N, 14.66. Found: C, 65.29; H, 6.46; N, 14.56.

***N*-(4-Fluorophenyl)-2-[1-(7-ethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4l)** Gray solid; yield 45%; mp 136–138°C; ^{1}H NMR: δ 1.26 (t, 3H, J = 7 Hz), 1.49 (s, 6H), 3.03 (s, 2H), 3.74 (q, 2H, J = 7 Hz), 4.73 (s, 2H), 5.23 (s, 2H), 6.77 (s, 1H), 7.12 (t, 2H, $J_{H\text{-}F}$ = 8 Hz), 7.35 (s, 1H), 7.43 (d, 2H, J = 8 Hz), 7.74 (s, 1H), 7.91 (s, 1H), 8.09 (s, 1H); ^{13}C NMR: δ 15.0, 28.4, 43.0, 54.3, 64.3, 89.8, 112.9, 115.8, 118.5, 122.4, 126.2, 127.5, 128.1, 128.5, 133.3, 137.9, 142.7, 144.0, 153.7, 154.8, 160.8, 169.8. Anal. Calcd for $C_{24}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98. Found: C, 61.56; H, 5.53; N, 14.88.

***N*-(4-Chlorophenyl)-2-[1-(7-ethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4m)** Gray solid; yield 43%; mp101–103°C; ^{1}H NMR: δ 1.47 (d, 3H, J = 7 Hz), 1.57 (s, 6H), 3.10 (s, 2H) 4.10 (m, 2H), 4.89 (s, 2H), 5.49 (s, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.31 (d, 2H, J = 8 Hz), 7.56 (d, 2H, J = 8 Hz), 7.94 (s, 1H), 8.32 (s, 1H), 9.14 (s, 1H). Anal. Calcd for $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47. Found: C, 59.46; H; 5.33; N, 14.40.

***N*-Benzyl-2-[1-(7-ethoxy-2,2-dimethyl-2,3-dihydroben-zofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4n)** Yellow solid; yield 41%; mp 86–88°C; ^{1}H NMR: δ 1.03 (t, 3H, J = 7 Hz), 1.51 (s, 6H), 3.01 (s, 2H), 4.11 (q, 2H, J = 7 Hz), 4.56 (d, 2H, J = 4 Hz), 4.85 (s, 2H), 5.44 (s, 2H), 7.00 (s, 1H), 7.07 (s, 1H), 7.24 (s, 1H), 7.27 (m, 2H), 7.29 (s, 2H), 7.99 (s, 1H), 8.23 (s, 1H); ^{13}C NMR: δ 13.7, 19.7, 24.3, 28.1, 43.3, 59.6, 73.7, 88.3, 111.1, 116.0, 121.0, 122.1, 124.8, 127.3, 127.7, 128.7, 131.1, 138.1, 144.0, 150.2, 152.0, 155.1, 167.2, 169.6. Anal. Calcd for $C_{25}H_{29}N_5O_4$: C, 64.78; H, 6.31; N, 15.11. Found: C, 64.68; H, 6.21; N, 15.01.

***N*-Cyclopropyl-2-[1-(7-propoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4o)** Gray solid; yield 38%; mp 95–97°C; ^{1}H NMR: δ 0.57 (t, 2H, J = 7 Hz), 0.81–1.00 (m, 2H), 1.50 (s, 6H), 1.83 (m, 2H), 2.77 (m, 1H), 3.01 (s, 2H), 4.00 (t, 2H, J = 7 Hz), 4.75 (s, 2H), 5.42 (s, 2H), 7.00 (s, 1H), 7.06 (s, 1H), 7.98 (s, 1H), 8.24 (s, 1H). Anal. Calcd for $C_{22}H_{29}N_5O_4$: C, 61.81; H, 6.84; N, 16.38. Found: C, 61.71; H, 6.74; N, 16.28.

***N*-Phenyl-2-[1-(7-propoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4p)** Yellow solid; yield 51%; mp 120–122°C; ^{1}H NMR: δ 0.99 (t, 3H, J = 7 Hz), 1.50 (s, 6H), 1.80 (q, 2H, J = 7 Hz), 3.00 (s, 2H), 3.98 (t, 2H,

J = 7 Hz), 4.89 (s, 2H), 5.48 (s, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.14 (t, 1H, *J* = 8 Hz), 7.34 (t, 2H, *J* = 8 Hz), 7.59 (d, 2H, *J* = 8 Hz), 7.97 (s, 1H), 8.32 (s, 1H), 9.05 (s, 1H); ^{13}C NMR: *δ* 10.6, 22.3, 28.2, 42.9, 43.4, 71.0, 74.0, 88.7, 111.4, 116.0, 120.8, 124.6, 124.7, 128.8, 128.8, 137.3, 140.7, 144.1, 146.7, 150.3, 152.4, 158.7, 161.4, 167.8. Anal. Calcd for $C_{25}H_{29}N_5O_4$: C, 64.78; H, 6.31; N, 15.11. Found: C, 64.63; H, 6.23; N, 15.01.

***N*-(4-Fluorophenyl)-2-[1-(7-propoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy] acetamide (4q)** White solid; yield 44%; mp 136–138°C; ^{1}H NMR: *δ* 1.00 (t, 3H, *J* = 7 Hz), 1.51 (s, 6H), 1.80 (m, 2H), 3.01(s, 2H), 3.99 (t, 2H, *J* = 7 Hz), 4.90 (s, 2H), 5.49 (s, 2H), 6.99 (s, 1H), 7.01 (s, 1H), 7.05 (d, 2H, *J* = 8 Hz), 7.43 (m, 2H), 7.93 (s, 1H), 8.36 (s, 1H), 9.15 (s, 1H); ^{13}C NMR: *δ* 10.4, 22.4, 28.2, 43.0, 43.3, 70.9, 73.9, 88.7, 111.4, 115.5, 115.7, 116.0, 122.0, 122.8, 124.5, 129.0, 133.3, 139.7, 144.2, 150.4, 152.1, 152.3, 157.0, 160.9, 167.9. Anal. Calcd for $C_{25}H_{28}FN_5O_4$: C, 62.36; H, 5.86; N, 14.54. Found: C, 62.26; H, 5.79; N 14.48.

***N*-(4-Chlorophenyl)-2-[1-(7-propoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy] acetamide (4r)** Yellow solid; yield 40%; mp 179–181°C; ^{1}H NMR: *δ* 1.00 (t, 3H, *J* = 7 Hz), 1.51 (s, 6H), 1.81 (m, 2H), 3.01 (s, 2H), 3.99 (t, 2H, *J* = 7 Hz), 4.90 (s, 2H), 5.49 (s, 2H), 7.02 (s, 1H), 7.08 (s, 1H), 7.30 (d, 2H, *J* = 8 Hz), 7.56 (d, 2H, *J* = 8 Hz), 7.97 (s, 2H), 9.14 (s, 1H); ^{13}C NMR: *δ* 10.7, 22.6, 28.2, 43.1, 43.3, 71.2, 74.2, 88.9, 111.3, 116.0, 122.3, 124.5, 128.9, 129.7, 136.0, 144.1, 150.3, 150.9, 152.4, 152.7, 160.3, 167.9. Anal. Calcd for $C_{25}H_{28}ClN_5O_4$: C, 60.30; H, 5.67; N, 14.06. Found: C, 60.23; H, 5.60; N, 14.00.

***N*-Benzyl-2-[1-(7-propoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4]triazol-1-yl-ethylideneaminooxy]acetamide (4s)** Yellow solid; yield 61%; mp 125–127°C; ^{1}H NMR: *δ*: 1.01 (t, 3H, *J* = 7 Hz), 1.50 (s, 6H), 1.80 (m, 2H), 2.99 (s, 2H), 3.99 (t, 2H, *J* = 7 Hz), 4.54 (d, 2H, *J* = 6 Hz), 4.84 (s, 2H), 5.37 (s, 2H), 6.93 (s, 1H), 7.04 (s, 1H), 7.25 (m, 5H), 7.96 (s, 1H), 8.15 (m, 1H). Anal. Calcd for $C_{26}H_{31}N_5O_4$: C, 65.39; H, 6.54; N, 14.66. Found: C, 65.31; H, 6.48; N, 14.58.

***N*-(Pyridin-2-yl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-[1,2,4-triazol-1-yl]ethylideneaminooxy] acetamide (4t)** White solid; yield 52%; mp 65–67°C; ^{1}H NMR: *δ* 1.50 (s, 6H), 2.20 (s, 6H), 2.99–3.01 (m, 2H), 3.84 (m, 3H), 4.90 (m, 2H), 5.46–5.49 (m, 2H), 7.06 (m, 3H), 7.68–7.71 (m, 1H), 8.26 (m, 4H), 9.67 (s, 1H); ^{13}C NMR: *δ* 28.2, 42.9, 43.5, 56.0, 74.0, 88.9, 109.4, 114.6, 116.3, 120.1, 125.0, 128.4, 138.2, 143.7, 144.8, 149.8, 151.1, 152.9, 168.3. HRMS. Calcd for $C_{22}H_{25}N_6O_4$, $(M+H)^+$: *m/z* 437.1893. Found: *m/z* 437.1932.

***N*-Phenyl-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1,2,4-triazol-1-yl)ethylideneaminooxy]propanamide (4u)** White solid; yield 55%; mp 66–68°C; ^{1}H NMR: *δ* 1.51 (s, 6H), 1.64 (d, 3H, *J* = 4.0 Hz), 3.02 (s, 2H), 3.84 (s, 3H), 5.00 (q, 1H, *J* = 4 Hz), 5.20 (d, 1H, *J* = 12 Hz), 5.78 (d, 1H, *J* = 12 Hz), 7.04 (s, 1H), 7.10 (s, 1H), 7.12 (t, 1H, *J* = 8 Hz), 7.33 (t, 2H, *J* = 4 Hz), 7.59 (d, 2H, *J* = 8 Hz), 7.95 (s, 1H), 8.22 (s, 1H), 8.89 (s, 1H); ^{13}C NMR: *δ* 17.6, 28.2, 43.0, 43.4, 56.0, 81.1, 88.9, 109.4, 116.1, 120.8, 124.6, 125.1, 128.5, 128.9, 137.6, 143.8, 144.9, 149.8, 152.0, 152.6, 170.7. HRMS. Calcd for $C_{24}H_{28}N_5O_4$, $(M+H)^+$: *m/z* 450.2063. Found: *m/z* 450.2130.

***N*-(2,6-Dimethylphenyl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1,2,4-triazol-1-yl) ethylideneaminooxy]propanamide (4v)** White solid; yield 46%; mp 79–81°C; ^{1}H NMR: *δ* 1.52 (s, 6H), 1.70 (d, 3H, *J* = 4 Hz), 2.16 (s, 6H), 3.02 (s, 2H), 3.86 (s, 3H), 5.05 (q, 1H, *J* = 4 Hz), 5.18 (d, 1H, *J* = 12 Hz), 5.78 (d, 1H, *J* = 12 Hz), 7.03 (d, 2H, *J* = 4 Hz), 7.05 (s, 1H), 7.09 (m, 1H), 7.57 (s, 1H), 8.18 (s, 1H), 8.66 (s, 1H); ^{13}C NMR: *δ* 17.8, 18.3, 28.2, 28.2, 42.9, 43.0, 56.0, 81.2, 88.9, 109.0, 115.9, 125.0, 127.3, 128.1, 128.3, 133.4, 135.6, 143.8, 144.9, 149.8, 151.6, 152.2, 171.3. HRMS. Calcd for $C_{26}H_{31}N_5O_4$, $(M+H)^+$: *m/z* 478.2376. Found: *m/z* 478.2445.

***N*-(4-Chlorophenyl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1H-1,2,4-triazol-1-yl)ethylideneaminooxy]propanamide (4w)** White solid; yield 40%; m.p. 68–70°C; ^{1}H NMR: *δ* 1.51 (s, 6H), 1.64 (d, 3H, *J* = 4 Hz), 3.02 (s, 2H), 3.85 (s, 3H), 5.00 (q, 1H, *J* = 4 Hz), 5.18 (d, 1H, *J* = 12 Hz), 5.78 (d, 1H, *J* = 12 Hz), 7.02 (s, 1H), 7.09 (s, 1H), 7.28 (d, 2H, *J* = 8 Hz), 7.55 (d, 2H, *J* = 8 Hz), 7.93 (s, 1H), 8.22 (s, 1H), 9.00 (s, 1H); ^{13}C NMR: *δ* 14.2, 17.6, 28.2, 43.0, 43.4, 56.1, 81.0, 89.0, 109.4, 116.0, 122.0, 125.0, 128.5, 128.9, 129.6, 136.3, 143.9, 144.9, 149.9, 152.0, 152.5, 170.9. HRMS. Calcd for $C_{24}H_{27}ClN_5O_4$, $(M+H)^+$: *m/z* 484.1673. Found: *m/z* 484.1741.

***N*-(Pyridin-2-yl)-2-[1-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1H-1,2,4-triazol-1-yl)ethylidene)amino) oxy]propanamide (4x)** White solid; yield 43%; mp 63–65°C; ^{1}H NMR: *δ* 1.51, (m, 6H), 1.65 (d, 3H, *J* = 4 Hz), 2.04 (s, 2H), 3.85 (s, 3H), 4.14 (q, 1H, *J* = 4 Hz), 5.34 (d, 1H, *J* = 12 Hz), 5.62 (d, 1H, *J* = 12 Hz), 7.05 (m, 1H), 7.07 (s, 1H), 7.27 (s, 1H), 7.71 (m, 1H), 8.14 (s, 1H), 8.23 (s, 1H), 8.24 (d, 1H, *J* = 8 Hz), 8.32 (s, 1H), 9.43 (s, 1H); ^{13}C NMR: *δ* 17.5, 28.2, 42.98, 43.7, 56.0, 81.0, 88.9, 109.5, 114.4, 116.3, 120.0, 125.2, 128.4, 138.2, 143.7, 144.7, 147.9, 149.7, 151.3, 152.7, 152.7, 171.2. HRMS. Calcd for $C_{23}H_{27}N_6O_4$, $(M+H)^+$: *m/z* 451.2016. Found: *m/z* 451.2072.

Crystal structure determination

The crystal of **3a** was analyzed at 150(2) K on a Bruker SMART CPEX 1000 CCD diffractometer equipped with a graphite-monochromatic MoKα (λ = 0.071073 nm) radiation source. The data were restored using Bruker's SCINTPLUS program [17], while the empirical absorption correction was performed using the SADABS procedure [18]. The structure was solved and refined by SHELXS-97 and SHELXL-97 [19]. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added according to theoretical models.

Fungicidal activity assay

The toxicities of compounds **4a–x** against 6 fungi were tested according to the Pesticide Biological Activity Evaluation Standard (SOP) [13]. The fungi were *Rhizoctonia* (*R. solani*), *Phytophythora capsici* (*P. capsici*), *Sclerotonia sclerotiorum* (*S. sclerotiorum*), *Gibberella zeae* (*G. zeae*), *Alternaria alternate* (*A. alternate*) and *Blumeria graminis* (*B. graminis*), *R. solani* and *B. graminis* were tested *in vivo* by a small plant assay at 500 mg/L, while *P. capsici*, *S. sclerotiorum*, *G. zeae* and *A. alternate* were tested by toxic medium method at 25 mg/L.

Funding: Natural Science Foundation of Hebei Province of China, Grant Number: H2018201273.

References

[1] Nevagi, R. J.; Dighe, S. N. Biological and medicinal significance of benzofuran. *Eur. J. Med. Chem.* **2015**, *97*, 561–581.

[2] Khanam, H.; Shamsuzzaman. Bioactive benzofuran derivatives: a review. *Eur. J. Med. Chem.* **2015**, *97*, 483–504.

[3] Wang, Y. M.; Zhao, J. Q.; Zhou, S. Y.; Yang, J. L.; Yao, X. J.; Tao, Y. D.; Mei, L. J.; Shi, Y. P. New sesquiterpenes and benzofuran derivatives from the aerial parts of Asterothamnus centraliasiaticus. *Tetrahedron* **2016**, *72*, 4910–4917.

[4] Kwiecie, H.; Goszczynska, A.; Rokosz, P. Benzofuran small molecules as potential inhibitors of human protein kinases. A Review. *Curr. Pharm. Design* **2016**, *22*, 879–894.

[5] Luo, X. F.; Hu, A. X.; Wang, Y.; Ye, J.; Wang, X. G.; Ou, X. M. Synthesis, crystal structure and insecticidal activity of 4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl) *N*-(aryl) thiazol-2-amine. *Chem. J. Chinese U.* **2011**, *32*, 2800–2805.

[6] Huang, Z. Q.; Cui, Q. M.; Xiong, L. X.; Wang, Z. W.; Wang, K. Y.; Zhao, Q. Q.; Bi, F. C.; Wang, Q. M. Synthesis and insecticidal activities and SAR studies of novel benzoheterocyclic diacylhydrazine derivatives. *J. Agric. Food Chem.* **2009**, *57*, 2447–2456.

[7] Lin, D.; Xiao, M. W.; Yang, Z. H.; Li, B. B.; Hu, A. X.; Ye, J. Synthesis and herbicidal activity of *N*-(2,2-dimethyl-7-alkoxy-2,3-dihydrobenzofuran-5-yl)-2-(4-arylxoyphen-oxy)propionamides. *Chem. Res. Chinese U.* **2017**, *33*, 74–79.

[8] Shen, F.; Hu, A. X.; Luo, X. F.; Ye, J.; Ou, X. M. Synthesis and bioactivity of (*E*)-2-benzylidenimino-4-(7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-y1) thiazole. *Chin. J. Org. Chem.* **2012**, *32*, 388–392.

[9] Arslan, T.; Keskin, S.; Demirayak, S. Synthesis and characterization of novel oxime derivatives. *Lett. Org. Chem*. **2016**, *13*, 672–677.

[10] Shilpa, M. S.; Ravindra, R. K.; Pramod, P. K.; Shrinivas, D. J.; Sheshagiri, R. D. Design, synthesis, docking and in vitro antifungal study of 1,2,4-triazole hybrids of 2-(aryloxy)quinolones. *Heterocycl. Commun.* **2017**, *23*, 317–324.

[11] Ahmed, S.; Zayed, M. F.; El-Messery, S. M.; Al-Agamy, M. H.; Abdel-Rahman, H. M. Design, synthesis, antimicrobial evaluation and molecular modeling study of 1,2,4-triazole-based 4-thiazolidinones. *Molecules* **2016**, *21*, 568.

[12] Maddila, S.; Pagadala, R.; Jonnalagadda, S. B. 1,2,4-Triazoles: a review of synthetic approaches and the biological activity. *Lett. Org. Chem*. **2013**, *10*, 693–714.

[13] Xuan, W. J. The synthesis and biology activity of 3,3-dimethyl-1-(1,2,4-triazol-1- yl)butan-2-one oxime ether acylamides. Master's Thesis Hunan Universtiy: Changsha, June **2011**.

[14] Li, W.; Tang, J. G.; Hu, A. X.; Ye, J.; Yang, Z. H.; Ou, X. M. Synthesis and fungicidal activity of 2-(2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-2-(1,2,4-triazole-1-methyl)- 1,3-dioxolane. *Chin. J. Org. Chem*. **2014**, *34*, 2272–2278.

[15] Li, W.; Yang, Z. H.; Hu, A. X.; Yan, X. W.; Ding, N.; Ye, J. Design, synthesis, and antitumor activity of (*E*,*Z*)-1-(dihydrobenzofuran-5-yl)-3-phenyl-2-(1,2,4-triazol-1-yl)-2-propen- 1-ones. *Chem. Biol. Drug Des.* **2015**, *86*, 1339–1350.

[16] Karakurt, A.; Aytemir, M. D.; Stables, J. P.; Ozalp, M.; Betül, K. F.; Ozbey, S.; Dalkara, S. Synthesis of some oxime ether derivatives of 1-(2-naphthyl)-2-(1,2,4-triazol-1-yl) ethanone and their anticonvulsant and antimicrobial activities. *Archiv. Der. Pharmazie* **2006**, *339*, 513–520.

[17] SAINI, Siemens. Analytical X-ray systems Inc.: Madison, Wisconsin, USA, 1996.

[18] Sheldrick, G. M. SADABS. Program for Empirical Absorption Correction of Area Detector Data; University of Gotingen: Germany, 1996.

[19] Sheldrick, G. M. SHELXTL V5.1, Software reference. Manual, Brucker AXS, Inc.: Madison, Wisconsin, USA, 1997.