Synthesis, Characterization and Antifungal Evaluation of Novel 2*H*-1,4-Benzoxazin-3(4*H*)-one Derivatives Linked with a 1,2,3-Triazole Moiety

Yuqin Jiang, Longfei Mao, Lin Zhu, Baoqi Ren, Wei Li, and Guiqing Xu

College of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, 453007, P. R. China

Reprint requests to Dr. Wei Li. Fax: +86-373-3329023. E-mail: 031172@htu.cn

Z. Naturforsch. **2014**, *69b*, 103 – 108 / DOI: 10.5560/ZNB.2014-3218
Received August 2, 2013

In order to obtain novel bioactive compounds with significant antifungal activities, a series of 2*H*-1,4-benzoxazin-3(4*H*)-one analogs linked with a 1,2,3-triazole moiety have been designed and synthesized *via* click reactions in a one-pot process at room temperature using CuCl as the catalyst. Their antifungal activities were tested against two plant-pathogenic fungi, Rhizoctonia cerealis (RC) and Colletotrichum capsici (CC). Statistical analysis showed that among the tested compounds in particular compound **3a** exhibits a significant growth inhibitory activity against both RC and CC. All the synthesized compounds have been characterized by IR, HRMS and NMR experiments.

Key words: 1,2,3-Triazole, 2*H*-1,4-Benzoxazin-3(4*H*)-one, Rhizoctonia Cerealis, Colletotrichum Capsici

Introduction

2*H*-1,4-Benzoxazin-3(4*H*)-one [1, 2] is an important heterocyclic scaffold. Molecules containing such a scaffold have been shown to exhibit a range of biological activities [3 – 7]. Among the examples shown in Fig. 1, compound A exhibits both thrombin inhibitory and fibrinogen receptor antagonistic activities [8]. Compound B is not only a novel antibacterial and antifungal (anti-candida) agent [9 – 11], but also a potential agent for treating anxiety, depression and negative symptoms in schizophrenia [12 – 14]. Compound C and other glycosides with the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton, which are isolated from gramineous plants, have been suggested to act as plant resistance factors against microbial diseases and insects [15]. Compound D is an inhibitor of bacterial histidine protein kinase [16, 17]. In recent years, in order to obtain all kinds of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives, different synthetic methods have been developed [18 – 22].

The 1,4-disubstituted 1,2,3-triazole derivatives have received much attention for their wide range of biological properties including that of a human β_3-adrenergic receptor agonist [23], and anti-microbial [24], anti-HIV [25], anti-convulsant [26], and anti-allergic effects [27]. As far as we know, the modification by introducing 1,2,3-triazole groups into 2*H*-1,4-benzoxazin-3(4*H*)-one has not been previously reported. The main purpose of this work is to synthesize a series of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives linked with a 1,2,3-triazole moiety. Their antifungal activities were assessed *in vitro* against two plant pathogenic fungi, CC and RC, while the antifungal agent diniconazole was used as a standard.

Results and Discussion

A one-pot synthesis, to improve the efficiency of a chemical reaction, is much desired because time- and chemical-consuming separation processes and purification of the intermediates are avoided. The key step for the synthesis of the target molecules is the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. One aim of this paper is to establish a one-pot reaction of 2*H*-1,4-benzoxazin-3(4*H*)-one (**1a**) [28] or 2*H*-1,4-benzoxazin-3(4*H*)-thione (**1b**) [29], propargyl bromide and substituted phenyl azides [30]. Initially, in order to optimize the reaction conditions, the reaction of **1a** (1 mmol), propar-

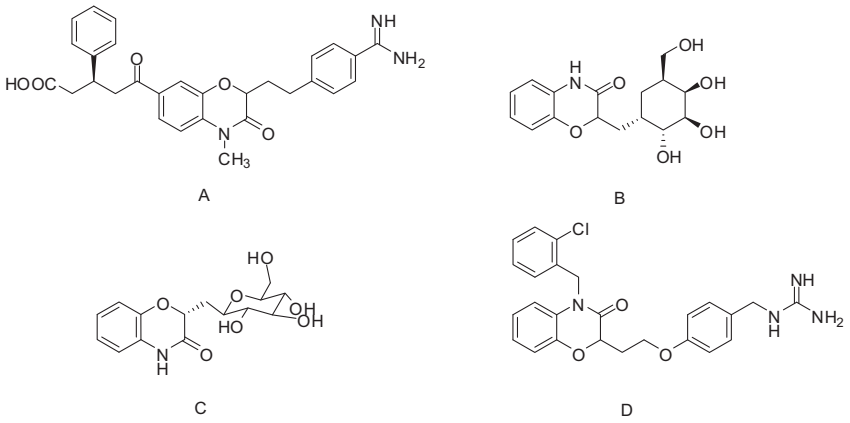
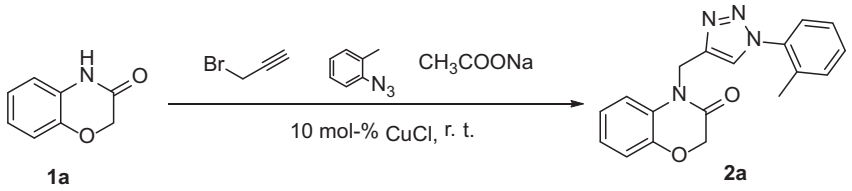


Fig. 1. Selected biologically important compounds containing a 2*H*-1,4-benzoxazin-3(4*H*)-one scaffold.



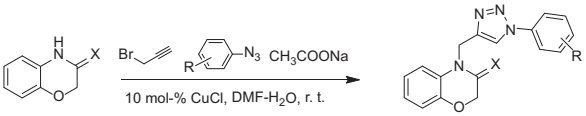
Scheme 1. The model reaction for the synthesis of **2a**.

gyl bromide (1 mmol) and 1-azido-2-methyl-benzene (1 mmol) in different co-solvents catalyzed by CuCl (10 mol-%) in the presence of sodium acetate (1 mmol) as the base at room temperature was selected as the model reaction (Scheme 1). Among the tested organic-water co-solvents, such as ethanol-water, acetone-water, DMF-water, and 1,4-dioxane-water, the model reaction in DMF-water (10 mL 1 : 1) showed the best results, and the yield was 85 % in 5 hours. Under the optimized reaction conditions, triazoles **2a**–**g** and **3a**–**e** were synthesized using **1a** or **1b** as the starting materials as shown in Table 1. All structures of the compounds synthesized were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS, and HR MS experiments.

In order to prove the significance of attaching a 1,2,3-triazole ring at the 2*H*-1,4-benzoxazin-3(4*H*)-one scaffold, compounds **2** and **3** were evaluated for their in *vitro* antifungal activities against two plant pathogenic fungi, CC and RC, taking diniconazole as the reference drug. Antifungal activity was evaluated by measuring fungal colonies in the presence of the tested compounds. This experiment was performed three times.

All compounds were tested at a concentration of 20 μg mL^{-1}, and the results are shown in Table 2. The

Table 1. 2*H*-1,4-Benzoxazin-3(4*H*)-one derivatives linked with a 1,2,3-triazole moiety (**2a**–**g, 3a**–**e**).



1a: X = O
1b: X = S
2a–**g**: X = O
3a–**e**: X = S

Entry	R	Yield (%)
2a	2-CH_3	85
2b	4-OH	86
2c	2-Cl	69
2d	3-OH	89
2e	4-CH_3	89
2f	2-F	88
2g	3-NO_2	88
3a	2-F	82
3b	2-CH_3	86
3c	2-Cl	79
3d	4-CH_3	81
3e	4-Cl	89

results revealed that most of the tested compounds displayed good inhibitory effects on the growth of the tested RC and CC strains. Among all the synthesized compounds, compound **3a** showed the best antifungal activities against RC and CC strains with 59 %

Table 2. Antifungal activity of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives, **1a** and diniconazole (DCL) at 20 μg mL^{-1}.

Fungi	Inhibitory ratio (%)													
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**3a**	**3b**	**3c**	**3d**	**3e**	**1a**	DCL
RC	47.1	11.8	5.9	5.7	29.4	0	41.2	58.8	52.9	54.1	29.4	53.7	13.3	95.2
CC	50.5	33.4	66.7	35.9	32.4	16.7	38.3	68.2	34.2	31.6	66.7	33.7	16.2	98.2

and 68 % inhibition, respectively. For CC strains, compounds **2c** and **3d** showed the same fungicidal activity with inhibition of 67 %, a slightly lower value than that of **3a**. Compounds **2b**, **2e**, **2f**, and **3d** showed poor fungicidal activities against the tested fungi (CC, RC) *in vitro*, and **2f** showed no antifungal activity against RC.

Compounds **2g**, **3b**, **3c**, and **3e** showed better activities against RC than CC. Compounds **2c** and **3d** showed better activities against CC than RC. All compounds showed better activities against CC strains than compound **1a**, indicating the significance of introducing a 1,2,3-trizaole moiety into **1a** and **1b**. It is worth mentioning that compounds synthesized from **1b** exhibit overall better fungicidal activities than the compounds from **1a**, which means that the element sulfur plays a significant role in enhancing the antifungal activities of the compounds against the two tested strains. Based on the results mentioned above, compound **3a** could be taken under consideration for further antifungal research.

Experimental Section

General Information

All chemicals were obtained from Tianjin Kermel Chemical Reagent Co., Ltd. and were used as received. All melting points were determined on a Yuhua X-3 melting point apparatus and are uncorrected. IR spectra were recorded on a Bio-rad FTS-40 spectrometer. ^{1}H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz spectrometer operating at 400.13 and 100.61 MHz, respectively. NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO at room temperature (20 ± 2 °C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. ESI MS were recorded on a Bruker Esquire 3000 instrument. High-resolution mass spectra (HR MS) were obtained from a MicrOTOF-Q II mass spectrometer with an ESI source (Waters, Manchester, UK).

*General procedure for the synthesis of the 1,4-benzoxazinon-derived aryl-1,2,3-triazoles (**2a–2g** and **3a–3e**)*

In a 50 mL round-bottom flask containing 20 mL of DMF-water (1 : 1 *v*/*v*), **1a** or **1b** (1 mmol), propargyl bromide (1 mmol), sodium acetate (1 mmol), substituted phenyl azide (1 mmol) and cuprous chloride (10 mol-%) were added and stirred at room temperature. After the reaction was finished (TLC control), the mixture was poured into water and extracted with chloroform. The resulting organic phase was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was then purified by column chromatography using ethyl acetate-hexane (1 : 15 *v*/*v*) as eluent to give the title compounds.

Fungicide screening

The tested two plant pathogenic fungi, CC and RC, were provided by the College of Life Science, Henan Normal University. The fungicidal activity was evaluated *in vitro* according to the literature procedures [31], fungicide diniconazole being used as a standard.

A stock solution of 200 μg mL^{-1} of each compound was prepared using DMSO as a solvent. A working solution (20 μg mL^{-1}) was prepared by diluting the stock solution (0.1 mL) with sterilized water (0.9 mL) in a 10 cm diameter Petri dish. Potato dextrose agar (PDA, 9 mL) was then added to prepare the plate. The plate was swirled to mix the compound into agar thoroughly under sterilized condition. After the agar had solidified, a fungi cake of 0.8 mm diameter was inoculated on each plate and cultured in the incubator at 28 °C. After 48 h, the diameter of fungi spread was measured. Growth inhibition was then calculated using the corresponding control. The*in vitro* inhibition percentages were also calculated.

*4-((1-o-Tolyl-1,2,3-triazol-4-yl)methyl)-2H-benzo[b]-[1,4]oxazin-3(4H)-one (**2a**)*

M. p. 161.1 – 162.4 °C. – IR (KBr): ν (cm^{-1}) = 3143, 1609, 1575, 1508, 1479, 1417, 1276, 1236, 1222, 1185, 1124, 1112, 1045, 1035, 1019, 991, 880, 817, 750. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H, CH), 7.61 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.39 – 7.27 (m, 4H, Ar-H), 7.09 – 6.97 (m, 3H, Ar-H), 5.28 (s, 2H, CH_2), 4.63 (s, 2H, CH_2), 2.18 (s, 3H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 146.3, 145.2, 136.3, 133.6, 131.5, 129.9, 128.7, 126.8, 125.9, 125.1, 124.3, 123.2, 116.9, 116.1, 67.8, 37.6, 17.9. – MS ((+)-ESI): *m*/*z*(%) = 321 (100) [M+H]$^+$. – HRMS ((+)-ESI): *m*/*z* = 343.1154 (calcd. 343.1158 for $C_{18}H_{16}N_4O_2$, [M+Na]$^+$).

*4-((1-(4-Hydroxyphenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2b**)*

M. p. 223.2 – 226.4 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3299$, 3134, 2848, 2704, 2599, 2332, 2108, 1877, 1667, 1601, 1521, 1504, 1474, 1417, 1373, 1359, 1322, 1276, 1223, 1127, 1059, 933, 830, 779, 756, 687, 658, 536, 523, 482, 453. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.93$ (s, 1H, OH), 8.52 (s, 1H, CH), 7.62 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.31 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.01 – 6.97 (m, 3H, Ar-H), 6.89 (d, $J = 8.8$ Hz, 2H, Ar-H), 5.20 (s, 2H, CH$_2$), 4.71 (s, 2H, CH$_2$). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 164.7$, 158.2, 145.3, 143.7, 129.1, 128.9, 124.1, 123.1, 122.3, 122.1, 116.9, 116.5, 116.3, 67.6, 36.8. – MS ((+)-ESI): $m/z(\%) = 323$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 345.0970$ (calcd. 345.0974 for $C_{17}H_{14}N_4O_3$, [M+Na]$^+$).

*4-((1-(2-Chlorophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2c**)*

M. p. 123.1 – 126.2 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3148$, 3089, 3061, 2919, 2851, 1685, 1604, 1592, 1503, 1468, 1448, 1405, 1375, 1356, 1310, 1284, 1258, 1230, 1128, 1072, 1035, 1017, 989, 932, 879, 769, 747, 695, 685, 553, 534, 485, 463. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.03$ (s, 1H, CH), 7.61 – 7.54 (m, 3H, Ar-H), 7.45 – 7.41 (m, 2H, Ar-H), 7.10 – 6.97 (m, 3H, Ar-H), 5.28 (s, 2H, CH$_2$), 4.62 (s, 2H, CH$_2$). – ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 164.9$, 145.2, 142.9, 134.8, 130.9, 130.8, 128.7, 128.6, 127.9, 127.7, 125.6, 124.3, 123.2, 116.9, 116.1, 67.8, 37.5. – MS ((+)-ESI): $m/z(\%) = 341$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 363.0619$ (calcd. 363.0619 for $C_{17}H_{13}ClN_4O_2$, [M+Na]$^+$).

*4-((1-(3-Hydroxyphenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2d**)*

M. p. 207.5 – 208.1 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3291$, 3157, 2917, 2848, 1661, 1618, 1501, 1473, 1421, 1337, 1282, 1252, 1217, 1175, 1159, 1127, 1058, 1044, 882, 779, 754, 679, 535, 458. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 10.01$ (s, 1H, OH), 8.64 (s, 1H, CH), 7.35 – 7.25 (m, 4H, Ar-H), 7.03 – 6.83 (m, 3H, Ar-H), 6.84 (d, $J = 8.0$ Hz, 1H, Ar-H), 5.21 (s, 2H, CH$_2$), 4.72 (s, 2H, CH$_2$). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 164.7$, 158.9, 154.5, 145.4, 143.9, 137.9, 131.2, 128.9, 124.2, 123.2, 122.1, 116.2, 116.1, 110.8, 107.4, 67.6, 36.7. – MS ((+)-ESI): $m/z(\%) = 323$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 345.0970$ (calcd. 345.0974 for $C_{17}H_{14}N_4O_3$, [M+Na]$^+$).

*4-((1-p-Tolyl-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2e**)*

M. p. 147.3 – 148.1 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3142$, 3085, 2919, 2851, 1682, 1605, 1503, 1471, 1403, 1323, 1282, 1131, 1057, 886, 815, 760, 537, 521. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.00$ (s, 1H, CH), 7.60 – 7.56 (m, 3H, Ar-H), 7.29 – 7.26 (m, 2H, Ar-H), 7.08 – 6.97 (m, 3H, Ar-H), 5.26 (s, 2H, CH$_2$), 4.64 (s, 2H, CH$_2$), 2.40 (s, 3H, CH$_3$). – ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 164.9$, 145.1, 143.8, 139.0, 134.6, 130.2, 128.7, 124.3, 123.2, 121.6, 120.4, 116.9, 116.1, 67.8, 37.6, 21.1. – MS ((+)-ESI): $m/z(\%) = 321$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 343.1171$ (calcd. 343.1158 for $C_{18}H_{16}N_4O_2$, [M+Na]$^+$).

*4-((1-(2-Fluorophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2f**)*

M. p. 104.3 – 105.9 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3143$, 1609, 1575, 1508, 1479, 1417, 1276, 1236, 1222, 1185, 1124, 1112, 1045, 1035, 1019, 991, 880, 817, 750. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.11$ (d, $J = 2.4$ Hz, 1H, CH), 7.92 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.59 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.45 – 7.40 (m, 1H, Ar-H), 7.32 – 7.27 (m, 2H, Ar-H), 7.09 – 6.98 (m, 3H, Ar-H), 5.28 (s, 2H, CH$_2$), 4.64 (s, 2H, CH$_2$). – ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 164.9$, 154.5, 152.1, 145.1, 130.4, 130.3, 128.6, 125.2, 125.1, 124.8, 124.3, 123.2, 117.1, 116.9, 115.9, 67.7, 37.4. – MS ((+)-ESI): $m/z(\%) = 325$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 347.0914$ (calcd. 347.0915 for $C_{17}H_{13}FN_4O_2$, [M+Na]$^+$).

*4-((1-(3-Nitrophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**2g**)*

M. p. 166.4 – 168.8 °C. – IR (KBr): $\nu\ (\mathrm{cm}^{-1}) = 3158$, 3113, 3077, 1682, 1606, 1593, 1539, 1504, 1467, 1398, 1354, 1315, 1280, 1256, 1243, 1127, 1051, 1039, 1021, 1007, 892, 875, 809, 757, 738, 669, 539. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.58$ (t, $J = 2.4$ Hz, 1H, Ar-H), 8.28 (dd, $J_1 = 1.20$ Hz, $J_2 = 8.4$ Hz, 1H, Ar-H), 8.18 (s, 1H, CH), 8.13 (dd, $J_1 = 1.2$ Hz, $J_2 = 8.4$ Hz, 1H, Ar-H), 7.73 (t, $J = 8.4$ Hz, 1H, Ar-H), 7.53 (dd, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, 1H, Ar-H), 7.08 – 6.98 (m, 3H, Ar-H), 5.78 (s, 2H, CH$_2$), 4.64 (s, 2H, CH$_2$). – ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 165.1$, 148.9, 145.1, 144.7, 137.6, 131.0, 128.5, 125.9, 124.5, 123.4, 123.3, 121.7, 117.1, 115.8, 115.3, 67.8, 37.4. – MS ((+)-ESI): $m/z(\%) = 368$ (100) [M+H]$^+$. – HRMS ((+)-ESI): $m/z = 374.0864$ (calcd. 347.0853 for $C_{17}H_{13}N_5O_5$, [M+Na]$^+$).

*4-((1-(2-Fluorophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazine-3(4H)-thione (**3a**)*

M. p. 70.8 – 72.5 °C. – IR (KBr): $\nu\,(\mathrm{cm}^{-1}) = 3143$, 1609, 1575, 1508, 1479, 1417, 1276, 1236, 1222, 1185, 1124, 1112, 1045, 1035, 1019, 991, 880, 817, 750. – ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.16$ (d, $J = 3.2$ Hz, 1H, CH), 7.94 (td, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, 1H, Ar-H), 7.43 – 7.38 (m, 1H, Ar-H), 7.33 – 7.23 (m, 3H, Ar-H), 7.10 – 7.06 (m, 1H, Ar-H), 7.06 – 6.96 (m, 1H, Ar-H), 6.88 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H, Ar-H), 4.60 (s, 2H, CH$_2$), 4.50 (s, 2H, CH$_2$).

– ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 154.5, 152.0, 146.2, 144.5, 133.7, 130.2, 130.1, 127.4, 125.7, 125.2, 125.1, 124.8, 124.4, 124.3, 122.6, 117.1, 115.9, 65.2, 23.5. – MS ((+)-ESI): m/z(%) = 341 (100) $[M+H]^+$. – HRMS ((+)-ESI): m/z = 363.0687 (calcd. 363.0692 for $C_{17}H_{13}FN_4OS$, $[M+Na]^+$).

*4-((1-o-Tolyl-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazine-3(4H)-thione (**3b**)*

M. p. 96.1 – 98.7 °C. – IR (KBr): ν (cm^{-1}) = 3143, 1609, 1576, 1508, 1479, 1417, 1276, 1236, 1222.5, 1185, 1125, 1112, 1045, 1035, 1019, 991, 880, 817, 750. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1H, CH), 7.41 – 7.27 (m, 5H, Ar-H), 7.08 (td, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 6.98 (td, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 6.88 (dd, J_1 = 1.3 Hz, J_2 = 7.9 Hz, 1H, Ar-H), 4.60 (s, 2H, CH_2), 4.52 (s, 2H, CH_2), 2.17 (s, 3H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 146.3, 144.1, 136.5, 133.8, 133.6, 131.5, 129.8, 127.4, 126.8, 126.0, 125.8, 124.5, 122.5, 115.9, 65.2, 23.6, 17.8. – MS ((+)-ESI): m/z(%) = 337 (100) $[M+H]^+$. – HRMS ((+)-ESI): m/z = 359.0945 (calcd. 359.0944 for $C_{18}H_{16}N_4OS$, $[M+Na]^+$).

*4-((1-(2-Chlorophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazine-3(4H)-thione (**3c**)*

M. p. 110.4 – 113.8 °C. – IR (KBr): ν (cm^{-1}) = 3143, 1609, 1575, 1508, 1479, 1417, 1276, 1236, 1222, 1185, 1124, 1113, 1045, 1035, 1019, 991, 880, 817, 751. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, CH), 7.63 – 7.61 (m, 1H, Ar-H), 7.56 – 7.54 (m, 1H, Ar-H), 7.44 – 7.42 (m, 2H, Ar-H), 7.29 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 7.08 (td, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 6.99 (td, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 6.88 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 4.60 (s, 2H, CH_2), 4.52 (s, 2H, CH_2). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 146.3, 144.1, 134.9, 133.8, 130.8, 130.7, 128.4, 127.9, 127.7, 127.4, 125.8, 125.2, 122.6, 115.9, 65.2, 23.6. – MS ((+)-ESI): m/z(%) = 357 (100) $[M+H]^+$. – HRMS ((+)-ESI): m/z = 379.0389 (calcd. 379.0389 for $C_{17}H_{13}ClN_4OS$, $[M+Na]^+$).

*4-((1-p-Tolyl-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazine-3(4H)-thione (**3d**)*

M. p. 118.2 – 120.7 °C. – IR (KBr): ν (cm^{-1}) = 3112, 3069, 2918, 1696, 1608, 1572, 1518, 1479, 1439, 1340, 1254, 1233, 1124, 1053, 1031, 1014, 989, 932, 876, 847, 816, 756, 739, 604, 531, 459. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H, CH), 7.56 (d, J = 8.0 Hz, 2H, Ar-H), 7.33 – 7.27 (m, 3H, Ar-H), 7.10 (t, J = 7.6 Hz, 1H, Ar-H), 7.03 – 6.98 (m, 1H, Ar-H), 6.89 (d, J = 7.6 Hz, 1H, Ar-H), 4.59 (s, 2H, CH_2), 4.52 (s, 2H, CH_2), 2.40 (s, 3H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 146.3, 144.8, 138.9, 134.7, 133.8, 130.2, 127.5, 125.7, 122.6, 121.2, 120.5, 115.9, 65.3, 23.6, 21.1. – MS ((+)-ESI): m/z(%) = 337 (100) $[M+H]^+$. – HRMS ((+)-ESI): m/z = 359.0944 (calcd. 359.0944 for $C_{18}H_{16}N_4OS$, $[M+Na]^+$).

*4-((1-(4-Chlorophenyl)-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazine-3(4H)-thione (**3e**)*

M. p. 99.9 – 101.4 °C. – IR (KBr): ν (cm^{-1}) = 3124, 3089, 1608, 1575, 1496, 1480, 1424, 1374, 1343, 1246, 1234, 1126, 1074, 1044, 1034, 1015, 988, 940, 878, 842, 765, 748, 724, 691, 613. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1H, CH), 7.64 (d, J = 7.6 Hz, 2H, Ar-H), 7.47 (d, J = 7.5 Hz, 2H, Ar-H), 7.31 (d, J = 6.8 Hz, 1H, Ar-H), 7.10 – 6.88 (m, 3H, Ar-H), 4.58 (s, 2H, CH_2), 4.52 (s, 2H, CH_2). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 146.3, 145.4, 135.5, 134.6, 133.8, 129.9, 127.6, 125.7, 122.7, 121.7, 121.1, 116.0, 65.2, 23.5. – MS ((+)-ESI): m/z(%) = 357 (100) $[M+H]^+$. – HRMS ((+)-ESI): m/z = 379.0405 (calcd. 379.0389 for $C_{17}H_{13}ClN_4OS$, $[M+Na]^+$).

Acknowledgement

The authors would like to thank the Natural Science Foundation of China (no. 21172058), the Foundation of the Henan Educational Committee (no. 14A350005), the Scientific Research Foundation for Doctors (no. 01036500508) and the Youth Foundation (2012QK11) of Henan Normal University for their financial support.

[1] B. Achari, S. B. Mandal, P. K. Dutta, C. Chowdhury, *Synlett* **2004**, *14*, 2449 – 2467.
[2] J. Ilaš, P. Š. Anderluh, M. S. Dolenc, D. Kikelj, *Tetrahedron* **2005**, *61*, 7325 – 7348.
[3] T. Besson, C. W. Rees, G. Cottenceau, A. M. Pons, *Bioorg. Med. Chem. Lett.* **1996**, *19*, 2343 – 2348.
[4] A. Fassihi, D. Abedi, L. Saghaie, R. Sabet, H. Fazeli, G. Bostaki, O. Deilami, H. Sadinpour, *Eur. J . Med. Chem.* **2009**, *44*, 2145 – 2157.
[5] E. Colson, J. Wallach, M. Hauteville, *Biochimie* **2005**, *87*, 223 – 230.
[6] G. J. Reddy, S. Sailaja, K. S. Rao, *Indian. J. Chem.* **2004**, *44B*, 204 – 206.
[7] A. D. Amar, M. S. Ranawat, *J. Chem. Pharm. Res.* **2012**, *4*, 1436 – 1440.
[8] P. Š. Anderluh, M. Anderluh, J. Ilaš, J. Mravljak, M. S. Dolenc, M. Stegnar, D. Kikelj, *J. Med. Chem.* **2005**, *48*, 3110 – 3113.

[9] E. Feng, H. Huang, Y. Zhou, D. Ye, H. L. Jiang, H. Liu, *J. Org. Chem.* **2009**, *74*, 2846 – 2849.
[10] R. Fringuelli, D. Pietrella, F. Schiaffella, A. Guarraci, S. Perito, F. Bistoni, A. Vecchiarelli, *Bioorg. Med. Chem.* **2002**, *10*, 1681 – 1686.
[11] A. Macchiarulo, G. Costantino, D. Fringuelli, A. Vecchiarelli, F. Schiaffella, R. Fringuelli, *Bioorg. Med. Chem.* **2002**, *10*, 3415 – 3423.
[12] S. M. Bromidge, B. Bertani, M. Borriello, A. Bozzoli, S. Faedo, M. Gianotti, L. G. Gordon, M. Hill, V. Zucchelli, J. M. Watson, L. Zonzini, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2338 – 2342.
[13] P. Smid, H. K. A. C. Coolen, H. G. Keizer, R. Hes, J. P. Moes, A. P. Hartog, B. Stork, R. H. Plekkenpol, L. C. Niemann, C. N. J. Stroomer, M. T. M. Tulp, H. H. Stuivenberg, A. C. McCreary, M. B. Hesselink, A. H. J. Herremans, C. G. Kruse, *J. Med. Chem.* **2005**, *48*, 6855 – 6869.
[14] L. A. Vliet, N. Rodenhuis, D. Dijkstra, H. Wikstrom, *J. Med. Chem.* **2000**, *43*, 2871 – 2882.
[15] H. M. Niemeyer, *Phytochemistry* **1988**, *27*, 3349 – 3358.
[16] R. Frechette, M. Beach, WO 9728167-A, **1997**.
[17] R. Frechette, M. A. Weidnerwells, WO 9717333-A, **1997**.
[18] F. L. Yin, G. F. Feng, Q. B. Song, C. Z. Qi, *J. Chem. Res.* **2012**, *36*, 41 – 44.
[19] Q. X. Hu, Z. M. Xia, L. Fan, J. N. Zheng, X. X. Wang, X. Lv, *Arkivoc* **2012**, *vi*, 129 – 142.
[20] K. E. O. Ylijoki, E. P. Kündig, *Chem. Commun.* **2011**, *47*, 10608 – 10610.
[21] D. B. Chen, G. D. Shen, W. L. Bao, *Org. Biomol. Chem.* **2009**, *7*, 4067 – 4073.
[22] M. Shariat, M. W. Samsudin, Z. Zakaria, *Chem. Cent. J.* **2013**, *7*, 58 – 63.
[23] L. L. Brockunier, E. R. Parmee, H. O. Ok, M. R. Candelore, M. A. Cascieri, L. F. Colwell, Jr., L. Deng, W. P. Fenney, M. J. Forrest, G. J. Hom, D. E. MacIntyre, L. Tota, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111 – 2114.
[24] M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. D. Reischer, D. Stapert, B. H. Yagi, *J. Med. Chem.* **2000**, *43*, 953 – 970.
[25] R. Alvarez, S. Velázquez, A. S. Félix, S. Aquaro, E. D. Clerq, C. F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185 – 4194.
[26] K. Danel, B. E. Pedersen, C. Nielsen, *J. Med. Chem.* **1998**, *41*, 191 – 198.
[27] D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1986**, *29*, 2269 – 2277.
[28] X. Huang, C. C. Chan, *Synthesis* **1984**, *10*, 851 – 853.
[29] H. Bartsch, T. Erker, G. Neubauer, *Monatsh. Chem.* **1988**, *119*, 1439 – 1444.
[30] V. R. Kamalraj, S. Senthil, P. Kannan, *J. Mol. Struct.* **2008**, *892*, 210 – 215.
[31] Z. J. Fan, Z. G. Shi, H. K. Zhang, X. F. Liu, L. L. Bao, L. Ma, X. Zuo, Q. X. Zheng, N. Mi, *J. Agr. Food Chem.* **2009**, *57*, 4279 – 4286.