RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, 7, 55288

Copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the synthesis of diverse 3-indolylbenzoxazin-2-ones: access to natural cephalandole A†

Rameshwar Prasad Pandit,[a] Jae-Jin Shim,[a] Sung Hong Kim[b]
and Yong Rok Lee*[a]

Received 26th September 2017
Accepted 28th November 2017

DOI: 10.1039/c7ra10634c

rsc.li/rsc-advances

A novel and facile copper-catalyzed direct coupling for the synthesis of diverse and functionalized 3-indolyl benzoxazin-2-ones from benzoxazin-2-ones and indoles has been developed. This new methodology offers an easy and rapid approach to a variety of 3-indolylbenzo[*b*][1,4]oxazin-2-ones in high yield. As an application of this protocol, a gram-scale synthesis of naturally occurring cephalandole A has also been accomplished.

Introduction

Benzoxazines and benzoxazin-2-ones are important heterocyclic compounds found in natural products and biologically active molecules (Fig. 1).[1,2] These compounds possess a wide range of pharmaceutical properties such as antihypertensive,[3] antifungal,[4] antimycobacterial,[5] anti-inflammatory,[6] bacterial histidine protein kinase inhibitory,[7] and D2 receptor antagonist activities.[8] In addition, compound **1** exhibits a potent effect of pyruvate kinase activators for the treatment of hereditary non-spherocytic hemolytic anemia and sickle cell anemia[9] and compound **2** is useful for the treatment of lung cancer.[10] Naturally occurring alkaloid, cephalandole A was originally isolated from Taiwanese orchid *Cephalanceopsis gracilis*[11] and its structure was later revised into 3 by organic structure determination using atomic resolution scanning probe microscopy.[12] Moreover, molecules bearing these skeletons have been also used as valuable building blocks for the synthesis of pharmaceuticals and photoactive materials.[13,14]

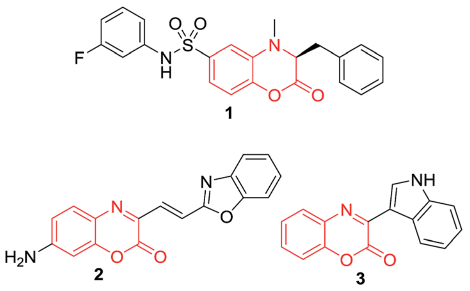


Fig. 1 Selected examples of naturally occurring and pharmaceutically active molecules bearing benzoxazin-2-one moiety.

Owing to the importance of benzoxazin-2-ones, several methods for their synthesis have been reported.[15,16] The general methods for benzoxazin-2-ones include the domino reaction of *o*-aminophenol with β-nitroacrylates,[17] cleavage of resin-bound pseudooxazolones with 2-aminophenols,[18] and TFA-catalyzed tandem reaction of benzoxazoles with 2-oxo-2-arylacetic acids.[19] In addition, enantioselective hydrogenation of benzoxazinones and enantioselective addition of indoles to ketimines to give chiral dihydrobenzoxazinones have been accomplished.[20,21]

Although several methodologies for the synthesis of benzoxazin-2-ones and dihydrobenzoxazinones have been developed, there are no reports on the direct coupling of benzoxazin-2-ones with indoles for the construction of 3-indolylbenzoxazin-2-ones so far. Recently, an iron-catalyzed oxidative sp^3 carbon–hydrogen bond functionalization of dihydrobenzoxazin-2-ones with indoles for the synthesis of 3-indolyldihydrobenzoxazin-2-ones has been described (Scheme 1a).[22] As a part of continuing efforts to develop new synthetic protocols for nitrogen heterocycles,[23] we herein report the copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the formation of diverse 3-indolyl benzoxazin-2-ones in air (Scheme 1b).

Results and discussion

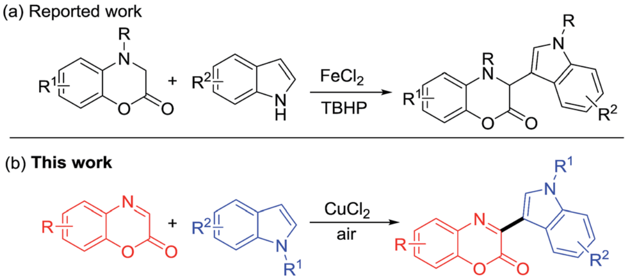
Our initial study commenced with the model reaction between benzoxazin-2-one **4a** and *N*-methylindole **5a** for the optimization of reaction condition (Table 1). Various metals were

---

[a] *School of Chemical Engineering, Yeungnam University, Gyeongsan, 38541, Republic of Korea. E-mail: yrlee@yu.ac.kr; Fax: +82-53-810-4631; Tel: +82-53-810-2529*

[b] *Analysis Research Division, Daegu Center, Korea Basic Science Institute, Daegu 41566, Republic of Korea*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra10634c



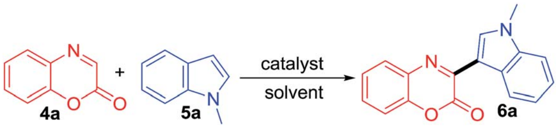
Scheme 1 Strategies for direct coupling of indoles to dihydrobenzoxazinones and benzoxazinones.

examined as catalysts under several solvents in air. When using 10 mol% of $CoCl_2$, $ZnCl_2$ and $NiCl_2$ at 80 °C for 24 h in dichloroethane, product **6a** was isolated in 32, 40, and 41% yields, respectively (entries 1–3, Table 1). Encouraged by these results, we screened other catalysts for the reaction. With 10 mol% of $FeCl_3$ and $CuCl_2$, the yield of **6a** increased to 80 and 89% respectively (entries 4–5). However, additional attempt using other copper catalysts such as CuF_2, $Cu(OAc)_2$, and $Cu(OTf)_2$, failed to further increase the yield (entries 6–8). Results of solvent screening showed that tetrahydrofuran (THF) was the best solvent (94%) among the solvents such as dioxane (87%), ethanol (66%), and water (60%) (entries 9–12). Changes in the loading of $CuCl_2$ to 5 mol%, 2 mol%, and 13 mol% did not improve the yield of **6a** (entries 13–15). In addition, the effect of temperature was next studied. It was found out that decreasing or increasing temperature decreased the yield of **6a** (entries 16 and 17). The structure of **6a** was determined by spectroscopic analysis. The ^1H NMR spectrum of **6a** showed a characteristic singlet singlet for indolyl C2 proton at δ 8.60 ppm and *N*-methyl peak on indolyl moiety at δ 3.85 ppm.

With the optimized reaction condition in hand, we further investigated the substrates scope employing different indoles **5b–5m** (Table 2). Reaction of **4a** with indoles **5b–5d** bearing *N*-ethyl, *N*-benzyl, and *N*-phenyl moieties provided the desired products **6b–6d** in 91, 67, and 72% yield, respectively. Treatment of **4a** with *N*-arylated indoles **5e–5g** having electron-donating or electron-withdrawing groups on the *N*-aryl ring, such as 4-Me, 4-OMe, and 4-Cl afforded the corresponding products **6e–6g** in 76%, 70%, and 77% yield, respectively. Indoles **5h–5l** bearing electron-donating or electron-withdrawing groups on the benzene ring were successful to afford the desired products. For example, reaction with *N*-methylindoles **5h–5i** bearing electron-donating groups like methyl at 5- and 6-position on the aryl ring provided **6h** (72%) and **6i** (70%), respectively. The reaction of *N*-methylindoles **5j–5l** bearing electron-withdrawing groups (5-F, 6-Cl, and 5-CO_2Me) afforded products **6j–6l** in 66, 61, and 78% yield, respectively.

To demonstrate the versatility of this coupling reaction, further reactions between various substituted benzoxazin-2-ones **4b–4g** and several *N*-substituted indoles **5a**, **5b**, **5d**, and **5g** were examined (Table 3). The reactions of **4b–4e** bearing electron-donating groups such as 6-methyl, 7-methyl, 6-*tert*-butyl, and 6-phenyl with *N*-substituted indoles **5a**, **5b**, **5d**, or **5g** provided products **7a–7g** in the range of 60–88% yield. The

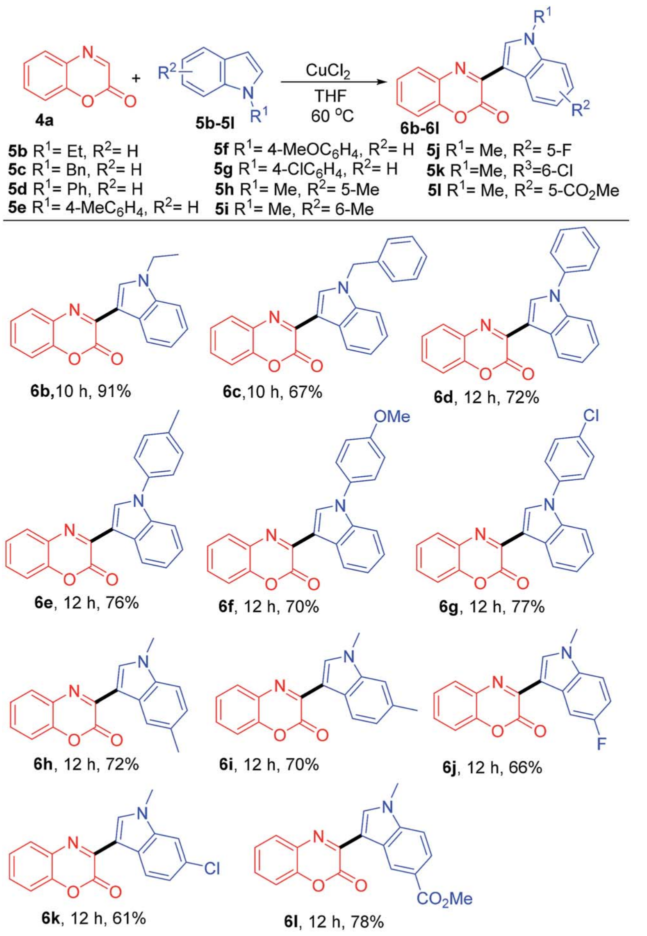
Table 1 Optimization of reaction condition for the synthesis of **6a**[a]



Entry	Catalyst	Solvent	Temp (°C)	Time [h]	Yield[b] [%]
1	$CoCl_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	32
2	$ZnCl_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	40
3	$NiCl_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	41
4	$FeCl_3$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	80
5	$CuCl_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	89
6	CuF_2 (10 mol%)	$ClCH_2CH_2Cl$	60	24	80
7	$Cu(OAc)_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	24	78
8	$Cu(OTf)_2$ (10 mol%)	$ClCH_2CH_2Cl$	60	12	85
9	$CuCl_2$ (10 mol%)	THF	60	12	94
10	$CuCl_2$ (10 mol%)	Dioxane	60	12	87
11	$CuCl_2$ (10 mol%)	EtOH	60	12	87
12	$CuCl_2$ (10 mol%)	H_2O	60	12	60
13	$CuCl_2$(5 mol%)	THF	60	12	91
14	$CuCl_2$ (2 mol%)	THF	60	24	78
15	$CuCl_2$ (13 mol%)	THF	60	6	82
16	$CuCl_2$ (10 mol%)	THF	50	12	90
17	$CuCl_2$ (10 mol%)	THF	70	10	85

[a] Reaction conditions: **4a** (0.5 mmol), **5a** (0.5 mmol), and catalyst (10 or 5 mol%) in solvent (3.0 mL) under air. [b] Yield of the isolated product **6a** after column chromatography.

Table 2 Formation of diverse 3-indolylbenzoxazine-2-ones **6b–6l** from **4a** with *N*-substituted indoles **5b–5l**[a]



[a] Reaction condition: **4a** (0.5 mmol), **5b–5l** (0.5 mmol), CuCl$_2$ (10 mol%), THF (3.0 mL), 60 °C, time (h), and isolated yield.

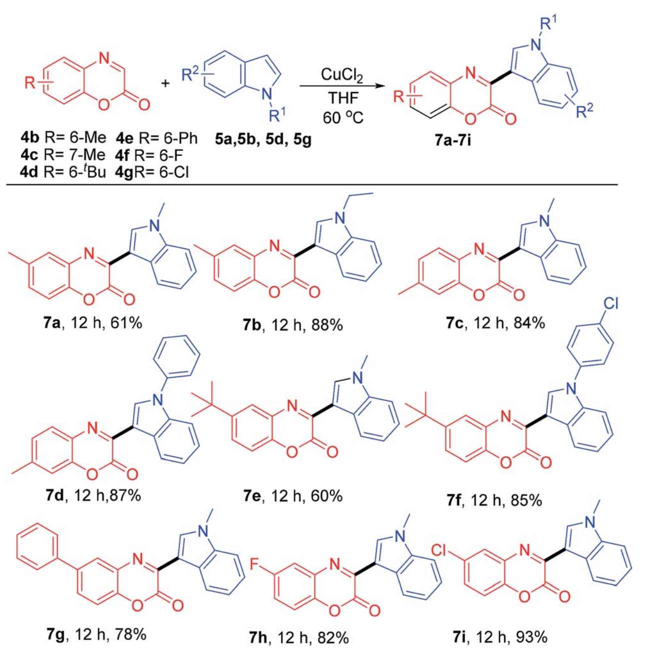
reactions of **4f** and **4g** bearing electron-withdrawing groups of 6-F and 6-Cl with **5a** afforded the products **7h** and **7i** in 82% and 93% yield, respectively.

The utility of this new methodology for the gram-scale synthesis of naturally occurring cephalandole A (**3**) was next demonstrated (Scheme 2). Upon treatment of **4a** with indole **5m** at 60 °C for 12 h in THF, **3** was obtained in 75% yield. This one-pot protocol has several advantages such as higher yield, fewer steps, and lower cost. The synthesized compound was confirmed to be natural product **3** by comparison of its spectroscopic data with those previously reported.[22]

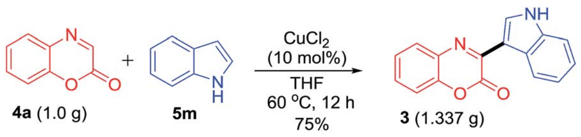
To elucidate the mechanism of this coupling reaction, we performed a control experiment (Scheme 3). The reaction between **4a** with **5a** in the absence of CuCl$_2$ in THF at room temperature for 30 h provided compound **8** in 93% yield. Further reaction of **8** in the presence of 10 mol% of CuCl$_2$ in THF at 60 °C for 1 h furnished **6a** in 96% yield. These results suggest that compound **8** might be the intermediate in the coupling reaction.

Based on the above experiment, the mechanism for the formation of **6a** is proposed as shown in Scheme 4. First, CuCl$_2$

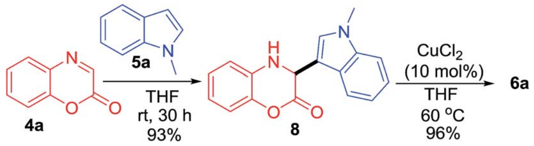
Table 3 Formation of diverse 3-indolylbenzoxazin-2-ones **7a–7i** from different benzoxazin-2-ones **4b–4g** with *N*-substituted indoles **5a**, **5b**, **5d**, or **5g**[a]



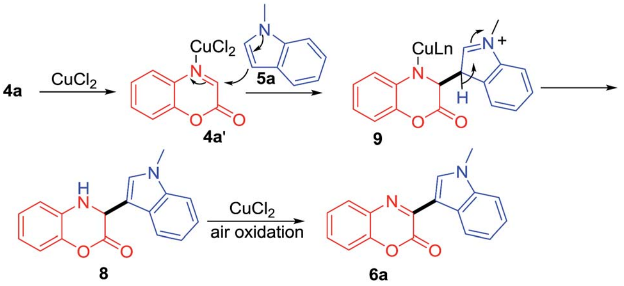
[a] Reaction condition: **4b–4g** (0.5 mmol), **5a**, **5b**, **5d**, **5g** (0.5 mmol), CuCl$_2$ (10 mol%), THF (3.0 mL), 60 °C, time (h), and isolated yields.



Scheme 2 One-pot gram-scale synthesis of natural alkaloid cephalandole A (**3**).



Scheme 3 Control experiments for **8** and **6a**.



Scheme 4 Proposed mechanism for the formation of **6a**.

catalyst binds to **4a** gives complex **4a′**, which subsequently undergoes nucleophilic attack by **5a** to give **9**. Deprotonation and protonation of **9** would afford intermediate **8**, which undergoes air oxidation to give **6a**[24]

Conclusions

In summary, a novel and efficient copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the synthesis of diverse and functionalized 3-indolylbenzoxazin-2-ones has been developed. This methodology provides a rapid synthetic route to natural cephalandole A and its derivatives. The proposed protocol has a wide substrate scope for both benzoxazin-2-ones and indoles.

Experimental

Imino cyclic esters were synthesized in the laboratory according to known procedure.[25] All indoles were prepared by either *N*-alkylation or *N*-arylation according to known method.[26] Solvents were used without further purification. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points are uncorrected and were determined on Fisher-Johns Melting Point Apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNS (600 and 150 MHz, respectively) spectrometer in $CDCl_3$ using $\delta = 7.24$ and 77.00 ppm as solvent chemical shift. Chemical shifts (δ) are expressed in units of ppm and coupling constants (J) values are given in Hz. Multiplicities are abbreviated as follows; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet and td = triplet of doublet. FT-IR (neat) spectra were recorded on ATR (PerkinElmer Spectrum 2) and HRMS was obtained on JEOL JMS-700 spectrometer at Korean Basic Science Institute.

General procedure for synthesis of 3-indolylbenzoxazin-2-ones

To the solution of imino cyclic esters (0.5 mmol) and indoles (0.5 mmol) in THF (3.0 mL), $CuCl_2$ (7 mg, 10 mol%) was added at room temperature and heated at 60 °C for 3–24 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 20 : 1) to afford the desired compounds.

3-(1-Methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6a). Prepared from **4a** (74 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 3 h as a yellow solid (130 mg, 94%); mp 195–197 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.87–8.83 (m, 1H), 8.60 (s, 1H), 7.85–7.82 (m, 1H), 7.38–7.32 (m, 5H), 7.27 (dd, $J = 7.2$, 1.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.70, 147.32, 145.01, 137.40, 137.12, 132.38, 128.52, 28.20, 127.02, 125.29, 123.53, 123.40, 122.19, 115.94, 110.48, 109.61, 33.47; ATR-IR (neat) 2927, 1728, 1531, 1077, 736 cm^{-1}; HRMS (EI) *m*/*z* (M^+) calcd for $C_{17}H_{12}N_2O_2$: 276.0899; found: 276.0901.

3-(1-Ethyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6b). Prepared from **4a** (74 mg, 0.5 mmol) and *N*-ethylindole **5b** (72 mg, 0.5 mmol) according to general procedure in 6 h as a yellow solid (132 mg, 91%); mp 180–182 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90–8.86 (m, 1H), 8.69 (s, 1H), 7.85 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.41–7.33 (m, 5H), 7.29–7.27 (m, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 1.55 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.76, 147.39, 145.03, 136.50, 135.60, 132.45, 128.51, 128.22, 127.26, 125.31, 123.68, 123.32, 122.15, 115.95, 110.62, 109.74, 41.78, 15.25; ATR-IR (neat) 2973, 1725, 1528, 1386, 737 cm^{-1}; HRMS (EI) *m*/*z* (M^+) calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1053.

3-(1-Benzyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6c). Prepared from **4a** (74 mg, 0.5 mmol) and *N*-benzylindole **5c** (104 mg, 0.5 mmol) according to general procedure in 6 h as a yellow solid (111 mg, 67%); mp 160–162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (d, $J = 7.8$ Hz, 1H), 8.75 (s, 1H), 7.87 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.41–7.25 (m, 9H), 7.17 (d, $J = 7.2$ Hz, 2H), 5.41 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.70, 147.44, 145.09, 136.95, 136.68, 136.17, 132.39, 128.94, 128.74, 128.31, 128.02, 127.30, 126.80, 125.36, 123.63, 123.61, 122.34, 116.01, 111.07, 110.34, 50.90; ATR-IR (neat) 2920, 1701, 1534, 1285, 739 cm^{-1}; HRMS (EI) *m*/*z* (M^+) calcd for $C_{23}H_{16}N_2O_2$: 352.1212; found: 352.1214.

3-(1-Phenyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6d). Prepared from **4a** (74 mg, 0.5 mmol) and *N*-phenylindole **5d** (96 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (121 mg, 72%); mp 169–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95 (d, $J = 8.4$ Hz, 1H), 8.87 (s, 1H), 7.89 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.58–7.53 (m, 5H), 7.45–7.72 (m, 1H), 7.41–7.36 (m, 3H), 7.34–7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.56, 147.38, 145.14, 138.57, 136.86, 135.87, 132.29, 129.76, 129.00, 128.43, 127.75, 127.43, 125.38, 124.91, 123.98, 123.70, 122.76, 116.03, 112.37, 110.92; ATR-IR (neat) 3056, 1734, 1531, 736 cm^{-1}; HRMS (EI) *m*/*z* (M^+) calcd for $C_{22}H_{14}N_2O_2$: 338.1055; found: 338.1052.

3-(1-(*p*-Tolyl)-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6e). Prepared from **4a** (74 mg, 0.5 mmol) and 1-(*p*-tolyl)-1*H*-indole **5e** (104 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (133 mg, 76%); mp 175–177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94 (d, $J = 7.8$ Hz, 1H), 8.84 (s, 1H), 7.89 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.36 (m, 7H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.60, 147.43, 145.15, 137.78, 137.04, 136.03, 132.35, 130.30, 128.91, 128.41, 127.37, 125.37, 124.80, 123.88, 123.65, 122.66, 116.03, 112.14, 110.97, 21.14; ATR-IR (neat) 3050, 1734, 1530, 1244, 1078, 741 cm^{-1}; HRMS (EI) *m*/*z* (M^+) calcd for $C_{23}H_{16}N_2O_2$: 352.1212; found: 352.1212.

3-(1-(4-Methoxyphenyl)-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6f). Prepared from **4a** (74 mg, 0.5 mmol) and 1-(4-methoxyphenyl)-1*H*-indole **5f** (111 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (128 mg, 70%); mp 148–150 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94 (d, $J = 8.4$ Hz, 1H), 8.81 (s, 1H), 7.89 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.47–7.44 (m, 3H), 7.41–7.36 (m, 3H), 7.33–7.29 (m, 2H), 7.06 (d, $J = 9.0$ Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.12, 152.61, 147.43, 145.13, 137.35, 136.22, 132.36, 131.46, 128.88, 128.39, 127.20, 126.40, 125.37, 123.85, 123.62, 122.61, 116.02, 114.86, 111.95, 110.87, 55.63; ATR-IR (neat) 2921, 1726, 1518, 1251, 739 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{23}H_{16}N_2O_3$: 368.1161; found: 368.1164.

3-(1-(4-Chlorophenyl)-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6g). Prepared from **4a** (74 mg, 0.5 mmol) and 1-(4-chlorophenyl)-1*H*-indole **5g** (114 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (143 mg, 77%); mp 209–211 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.94 (d, *J* = 7.8 Hz, 1H), 8.82 (s, 1H), 7.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55–7.48 (m, 5H), 7.44–7.37 (m, 3H), 7.35–7.33 (m, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.55, 147.27, 145.17, 137.12, 136.73, 135.48, 133.48, 132.24, 129.99, 129.22, 128.51, 127.46, 126.13, 125.46, 124.21, 123.84, 122.95, 116.09, 112.72, 110.66; ATR-IR (neat) 2921, 1729, 1535, 1087, 740 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{22}H_{13}ClN_2O_2$: 372.0666; found: 372.0664.

3-(1,5-Dimethyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6h). Prepared from **4a** (74 mg, 0.5 mmol) and 1,5-dimethyl-1*H*-indole **5h** (72 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (104 mg, 72%); mp 220–222 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.64 (s, 1H), 8.57 (s, 1H), 7.87–7.86 (m, 1H), 7.37–7.35 (m, 2H), 7.28–7.24 (m, 2H), 7.16 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.83 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.74, 147.36, 144.96, 137.20, 135.79, 132.42, 131.80, 128.35, 128.14, 127.22, 125.23, 124.86, 123.22, 115.91, 110.03, 109.29, 33.50, 21.80; ATR-IR (neat) 2916, 1729, 1525, 1366, 744 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1052.

3-(1,6-Dimethyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6i). Prepared from **4a** (74 mg, 0.5 mmol) and 1,6-dimethyl-1*H*-indole **5i** (72 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (101 mg, 70%); mp 210–212 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.69 (d, *J* = 7.8 Hz, 1H), 8.52 (s, 1H), 7.83–7.80 (m, 1H), 7.37–7.31 (m, 2H), 7.26–7.24 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 3.81 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.69, 147.25, 144.98, 137.79, 136.75, 133.38, 132.42, 128.35, 128.14, 125.22, 124.78, 123.80, 123.17, 115.89, 110.48, 109.66, 33.37, 21.85; ATR-IR (neat) 2924, 1726, 1528, 1067, 746 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1056.

3-(5-Fluoro-1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6j). Prepared from **4a** (74 mg, 0.5 mmol) and 5-fluoro-1-methyl-1*H*-indole **5j** (75 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (97 mg, 66%); mp 218–220 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.60 (s, 1H), 8.51 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.83 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.40–7.34 (m, 2H), 7.28–7.23 (m, 2H), 7.06 (td, *J* = 9.0, 3.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 159.52 (d, *J* = 253.2 Hz), 152.60, 147.08, 145.00, 138.12, 133.94, 132.22, 128.75, 128.25, 127.63, 127.55, 125.41, 115.97, 111.56 (d, *J* = 26.4 Hz), 110.31 (d, *J* = 9.7 Hz), 108.98 (d, *J* = 25.3 Hz), 33.76; ATR-IR (neat) 1726, 1529, 1062, 791 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{17}H_{11}FN_2O_2$: 394.0805; found: 294.0809.

3-(6-Chloro-1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (6k). Prepared from **4a** (74 mg, 0.5 mmol) and 6-chloro-1-methyl-1*H*-indole **5k** (83 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (95 mg, 61%); mp 241–243 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.76 (d, *J* = 8.4 Hz, 1H), 8.59 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.41–7.32 (m, 3H), 7.30–7.27 (m, 1H), 7.24 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.59, 147.09, 145.10, 137.93, 137.51, 132.22, 129.44, 128.95, 128.31, 125.53, 125.43, 124.52, 122.68, 116.04, 110.62, 109.82, 33.59; ATR-IR (neat) 1728, 1528, 1452, 918, 746 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{17}H_{11}ClN_2O_2$: 310.0509; found: 310.0508.

Methyl 1-methyl-3-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3-yl)-1*H*-indole-5-carboxylate (6l). Prepared from **4a** (74 mg, 0.5 mmol) and methyl 1-methyl-1*H*-indole-5-carboxylate **5l** (95 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (130 mg, 78%); mp 240–242 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.54 (d, *J* = 1.2 Hz, 1H), 8.65 (s, 1H), 8.04 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.43–7.36 (m, 3H), 7.29 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.02, 152.55, 146.91, 145.08, 139.82, 138.06, 132.15, 129.13, 128.64, 126.55, 126.31, 125.44, 124.79, 124.03, 115.97, 111.50, 109.36, 52.04, 33.65; ATR-IR (neat) 1734, 1531, 1456, 1078, 738 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{19}H_{14}N_2O_4$: 334.0954; found: 334.0958.

6-Methyl-3-(1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7a). Prepared from 6-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one **4b** (81 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (88 mg, 61%); mp 218–220 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.88–8.85 (m, 1H), 8.61 (s, 1H), 7.65 (s, 1H), 7.38–7.32 (m, 3H), 7.19–7.15 (m, 2H), 3.87 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.95, 147.29, 143.00, 137.42, 137.01, 135.11, 132.10, 129.54, 128.16, 127.07, 123.56, 123.36, 122.13, 115.52, 110.58, 109.60, 33.48, 20.89; ATR-IR (neat) 2908, 1735, 1498, 739 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1053.

3-(1-Ethyl-1*H*-indol-3-yl)-6-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one (7b). Prepared from 6-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one **4b** (81 mg, 0.5 mmol) and *N*-ethylindole **5b** (72 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (133 mg, 88%); mp 184–186 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.90–8.86 (m, 1H), 8.66 (s, 1H), 7.64 (s, 1H), 7.40–7.37 (m, 1H), 7.34–7.31 (m, 2H), 7.18–7.14 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.54 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.91, 147.26, 142.95, 136.44, 135.41, 135.05, 132.10, 129.44, 128.13, 127.25, 123.70, 123.20, 122.03, 115.47, 110.66, 109.66, 41.70, 20.86, 15.22; ATR-IR (neat) 1725, 1528, 1370, 1055, 744 cm^{-1}; HRMS (EI) *m*/*z* (M$^+$) calcd for $C_{19}H_{16}N_2O_2$: 304.1212; found: 304.1216.

7-Methyl-3-(1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7c). Prepared from 7-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one **4c** (81 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (122 mg, 84%); mp 216–218 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.85–8.82 (m, 1H), 8.55 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.36–7.31 (m, 3H), 7.16–7.13 (m, 1H), 7.05 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.85, 146.36, 144.86, 139.53, 137.34, 136.64, 130.29, 127.80, 126.98, 126.37, 123.47, 123.25, 121.99, 116.03, 110.48, 109.51, 33.39, 21.54; ATR-IR (neat) 1721, 1530, 1051, 741 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1052.

7-Methyl-3-(1-phenyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7d). Prepared from 7-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one **4c** (81 mg, 0.5 mmol) and *N*-phenylindole **5d** (96 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (153 mg, 87%); mp 140–142 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.93 (d, $J = 7.8$ Hz, 1H), 8.82 (s, 1H), 7.75 (d, $J = 7.8$ Hz, 1H), 7.57–7.52 (m, 5H), 7.44–7.41 (m, 1H), 7.36 (t, $J = 7.2$ Hz, 1H), 7.31 (td, $J = 7.8$, 1.2, 1H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.08 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.72, 146.36, 145.00, 140.08, 138.64, 136.77, 135.38, 130.22, 129.72, 128.02, 127.62, 127.43, 126.47, 124.86, 123.84, 123.67, 122.59, 116.12, 112.40, 110.82, 21.60; ATR-IR (neat) 3051, 1738, 1514, 1228, 736 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{23}H_{16}N_2O_2$: 352.1212; found: 352.1214.

6-(*tert*-Butyl)-3-(1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7e). Prepared from 6-(*tert*-butyl)-2*H*-benzo[*b*][1,4]oxazin-2-one **4d** (101 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (98 mg, 60%); mp 185–187 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.90–8.88 (m, 1H), 8.60 (s, 1H), 7.84 (d, $J = 2.4$ Hz, 1H), 7.42 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.38–7.32 (m, 3H), 7.20 (d, $J = 9.0$ Hz, 1H), 3.85 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.96, 148.63, 147.15, 142.78, 137.37, 137.00, 131.77, 127.01, 126.13, 124.75, 123.54, 123.33, 122.10, 115.29, 110.51, 109.57, 34.64, 33.43, 31.45; ATR-IR (neat) 2952, 1727, 1526, 1369, 1074, 741 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{21}H_{20}N_2O_2$: 332.1525; found: 332.1527.

6-(*tert*-Butyl)-3-(1-(4-chlorophenyl)-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7f). Prepared from 6-(*tert*-butyl)-2*H*-benzo[*b*][1,4]oxazin-2-one **4d** (101 mg, 0.5 mmol) and 1-(4-chlorophenyl)-1*H*-indole **5g** (114 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (181 mg, 85%); mp 208–210 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.96 (d, $J = 7.8$ Hz, 1H), 8.80 (s, 1H), 7.87 (d, $J = 1.8$ Hz, 1H), 7.53–7.45 (m, 6H), 7.40 (t, $J = 7.2$ Hz, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.76, 148.80, 147.05, 142.91, 137.13, 136.62, 135.26, 133.33, 131.68, 129.93, 127.48, 126.81, 126.04, 125.03, 124.10, 123.84, 122.83, 115.41, 112.76, 110.58, 34.67, 31.45; ATR-IR (neat) 2958, 1727, 1528, 1217, 742 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{26}H_{21}ClN_2O_2$: 428.1292; found: 428.1289.

3-(1-Methyl-1*H*-indol-3-yl)-6-phenyl-2*H*-benzo[*b*][1,4]oxazin-2-one (7g). Prepared from 6-phenyl-2*H*-benzo[*b*][1,4]oxazin-2-one **4e** (112 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (137 mg, 78%); mp 236–238 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.91–8.88 (m, 1H), 8.63 (s, 1H), 8.05 (d, $J = 3.6$ Hz, 1H), 7.67 (d, $J = 7.2$ Hz, 2H), 7.60 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.48 (t, $J = 7.2$ Hz, 2H), 7.40–7.34 (m, 4H), 7.33 (d, $J = 8.4$ Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.70, 147.60, 144.38, 139.75, 138.69, 137.45, 137.25, 132.54, 128.93, 127.62, 127.33, 127.13, 127.06, 126.42, 123.59, 123.47, 122.27, 116.21, 110.55, 109.66, 33.52; ATR-IR (neat) 3055, 1743, 1515, 1240, 735 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{23}H_{16}N_2O_2$: 352.1212; found: 352.1210.

6-Fluoro-3-(1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7h). Prepared from 6-fluoro-2*H*-benzo[*b*][1,4]oxazin-2-one **4f** (82 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (120 mg, 82%); mp 245–247 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.81–8.79 (m, 1H), 8.63 (s, 1H), 7.51 (dd, $J = 9.0$, 3.0 Hz, 1H), 7.39–7.33 (m, 3H), 7.22 (dd, $J = 9.0$, 4.8 Hz, 1H), 7.10–7.05 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 159.58 (d, $J = 242.4$ Hz), 152.42, 148.02, 141.30, 137.74, 137.47, 133.01 (d, $J = 11.8$ Hz), 126.97, 123.62, 123.54, 122.47, 116.76 (d, $J = 9.4$ Hz), 115.57 (d, $J = 24.6$ Hz), 113.71 (d, $J = 23.5$ Hz), 110.41, 109.73, 33.57; ATR-IR (neat) 1733, 1523, 1371, 1244, 1078, 742 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{17}H_{11}FN_2O_2$: 294.0805; found: 294.0804.

6-Chloro-3-(1-methyl-1*H*-indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one (7i). Prepared from 6-chloro-2*H*-benzo[*b*][1,4]oxazin-2-one **4g** (91 mg, 0.5 mmol) and *N*-methylindole **5a** (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (144 mg, 93%); mp 228–230 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.81–8.78 (m, 1H), 8.63 (s, 1H), 7.81 (d, $J = 1.2$ Hz, 1H), 7.39–7.33 (m, 3H), 7.30 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.19 (d, $J = 8.4$ Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 152.22, 148.03, 143.57, 137.73, 137.47, 133.09, 130.36, 128.20, 127.54, 126.97, 123.66, 123.58, 122.51, 116.98, 110.44, 109.74, 33.59; ATR-IR (neat) 1729, 1530, 1459, 1069, 743 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{17}H_{11}ClN_2O_2$: 310.0509; found: 310.0508.

Gram-scale synthesis of cephalandole A

The solution of 2*H*-benzo[*b*][1,4]oxazin-2-one **4a** (1.0 gram, 6.80 mmol) and indole **5m** (0.81 gram, 6.80 mmol) in THF (15 mL), CuCl$_2$ (48 mg, 10 mol%) was added at room temperature and heated at 60 °C for 12 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 5 : 1) to afford cephalandole A (**3**, 1.337 gram, 75%); mp 237–239 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 11.07 (s, 1H), 8.89 (dd, $J = 6.6$, 4.8 Hz, 1H), 8.82 (d, $J = 3.0$ Hz, 1H), 7.89 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.59–7.55 (m, 1H), 7.49 (td, $J = 7.8$, 1.8 Hz, 1H), 7.43 (td, $J = 7.8$, 1.8 Hz, 1H), 7.35 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.30–7.26 (m, 2H); ^{13}C NMR (150 MHz, acetone-d_6) δ 152.95, 149.01, 146.19, 137.82, 134.53, 133.17, 129.53, 128.83, 127.32, 126.07, 124.13, 124.05, 122.43, 116.71, 112.72, 112.33; ATR-IR (neat) 3285, 1715, 1602, 1530, 1429 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{16}H_{10}N_2O_2$: 262.0742; found: 262.0740.

Control experiments

The solution of **4a** (147 mg, 1.0 mmol) and *N*-methylindole **5a** (130 mg, 1.0 mmol) in THF (3.0 mL) was stirred at room temperature 30 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 5 : 1) to afford **8** as a solid (258 mg, 93%); mp 170–172 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.67 (d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.26–7.23 (m, 1H), 7.16–7.13 (m, 1H), 7.07 (dd, $J =$

7.8, 1.2 Hz, 1H), 7.00 (td, $J = 7.8$, 1.2 Hz, 1H), 6.98 (s, 1H), 6.87 (td, $J = 7.8$, 1.2 Hz, 1H), 6.76 (dd, $J = 7.8$, 1.2 Hz, 1H), 5.33 (s, 1H), 3.70 (s, 4H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.15, 141.31, 137.10, 132.83, 127.74, 125.99, 124.99, 122.42, 120.36, 119.99, 119.24, 116.89, 115.04, 109.69, 109.63, 52.56, 32.89; ATR-IR (neat) 3346, 1735, 1529, 1119, 737 cm^{-1}; HRMS (EI) m/z (M$^+$) calcd for $C_{17}H_{14}N_2O_2$: 278.1055; found: 278.1058.

To the solution of **8** (139 mg, 0.5 mmol) in THF (3.0 mL), CuCl$_2$ (7 mg, 10 mol%) was added at room temperature and heated at 60 °C for 1 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 20 : 1) to afford **6a** as a solid (132 mg, 96%).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the Nano Material Technology Development Program of the Korean National Research Foundation (NRF) funded by the Korean Ministry of Education, Science, and Technology (2012M3A7B4049675) and Priority Research Centers Program (2014R1A6A1031189).

Notes and references

1 (*a*) *Antibiotics and Antiviral Compounds*, ed. K. Krohn, H. A. Kirst and H. Maag, VCH, Weinheim, 1993; (*b*) *Pharmaceutical Substances*, ed. A. Kleemann, J. Engel, B. Kutscher and D. Reichert, Thieme, Stuttgart, New York, 4th edn, 2001; (*c*) *Houben-Weyl Methods of Organic Chemistry, Hetarenes IV, Six-Membered and Large Hetero-Rings with Maximum Unsaturation*, ed. J. Teller and E. Schaumann, Georg Thieme, Stuttgart, 1997, vol. E9a, pp. 141–177; (*d*) J. Ilaš, P. S. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325; (*e*) B. Achari, S. B. Mandal, P. K. Dutta and C. Chowdhury, *Synlett*, 2004, 2449.

2 (*a*) T. Hasui, N. Matsunaga, T. Ora, N. Ohyabu, N. Nishigaki, Y. Imura, Y. Igata, H. Matsui, T. Motoyaji, T. Tanaka, N. Habuka, S. Sogabe, M. Ono, C. S. Siedem, T. P. Tang, C. Gauthier, L. A. DeMeese, S. A. Boyd and S. Fukumoto, *J. Med. Chem.*, 2011, **54**, 8616; (*b*) H. Matsuoka, N. Maruyama, K. Tsuji, N. Kato, T. Akimoto, Y. Takeda, K. Yano and T. Kuroki, *J. Med. Chem.*, 1997, **40**, 105; (*c*) S. M. Bromidge, B. Bertani, M. Borriello, S. Faedo, L. J. Gordon, E. Granci, M. Hill, H. R. Marshall, L. P. Stasi, V. Zucchelli, G. Merlo, A. Vesentini, J. M. Watson and L. Zonzini, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5653; (*d*) S. M. Bromidge, B. Bertani, M. Borriello, A. Bozzoli, S. Faedo, M. Gianotti, L. J. Gordon, M. Hill, V. Zucchelli, J. M. Watson and L. Zonzini, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2338; (*e*) T. Hasui, T. Ohra, N. Ohyabu, K. Asano, H. Matsui, A. Mizukami, N. Habuka, S. Sogabe, S. Endo, C. S. Siedem, T. P. Tang, C. Gauthier, L. A. De Meese, S. A. Boyd and S. Fukumoto, *Bioorg. Med. Chem.*, 2013, **21**, 5983.

3 F. Touzeau, A. Arrault, G. Guillaumet, E. Scalbert, B. Pfeiffer, M.-C. Rettori, P. Renard and J.-Y. Mérour, *J. Med. Chem.*, 2003, **46**, 1962.

4 K. Waisser, L. Kubicová, V. Buchta, P. Kubanová, K. Bajerová, L. Jirásková, O. Bednařík, O. Bureš and P. Holý, *Folia Microbiol.*, 2002, **47**, 488.

5 (*a*) K. Waiser, M. Peřina, J. Kuneš, V. Klimešová and J. Kaustová, *Il Farmaco*, 2003, **58**, 1137; (*b*) S. Konda, S. Raparthi, K. Bhaskar, R. K. Munagati, V. Guguloth, L. Nagarapu and D. M. Akkerwar, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1643.

6 (*a*) A. Khalaj, M. Abdollahi, A. Kebriaeezadeh, N. Adibpour, Z. Pandi and S. Rasoulamini, *Indian J. Pharmacol.*, 2002, **34**, 184; (*b*) I. V. Mashevakaya, L. V. Anikina, Y. B. Vikharev, V. A. Safin, S. V. Koltsova and A. N. Maslivets, *Pharm. Chem. J.*, 2001, **35**, 414.

7 R. Frechette and M. A. Weidner-Wells, WO Patent Appl. 9717333, 1997.

8 L. D. Wise, D. J. Wustrow and T. Belliotti, WO Patent Appl. 9745419, 1997.

9 S. U. S.-S. Michael, WO Patent 2012151440, 2012.

10 C. Li and G. Xiaoxia, Patent CN 103664919 A, 2014.

11 (*a*) P.-L. Wu, Y.-L. Hsu and C.-W. Jao, *J. Nat. Prod.*, 2006, **69**, 1467; (*b*) Y.-T. Wu, Y.-L. Hsu and P.-L. Wu, *Heterocycles*, 2008, **75**, 1191.

12 (*a*) J. J. Mason, J. Bergman and T. Janosik, *J. Nat. Prod.*, 2008, **71**, 1447; (*b*) L. Gross, F. Mohn, N. Moll, G. Meyer, W. M. Abdel-Megeed and M. Jaspars, *Nat. Chem.*, 2010, **2**, 821.

13 (*a*) Q. Chen, M. Chen, C. Yu, L. Shi, D. Wang, Y. Yang and Y. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (*b*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 6751; (*c*) C. Saitz, H. Rodŕıguez, A. Márquez, A. Cánete, C. Jullian and A. Zanocco, *Synth. Commun.*, 2001, **31**, 135; (*d*) H. Miyabe, Y. Yamaoka and Y. Takemoto, *J. Org. Chem.*, 2006, **71**, 2099.

14 (*a*) R. A. Duval, G. Lewin, E. Peris, N. Chahboune, A. Garofano, S. Drçse, D. Cortes, U. Brandt and R. Hocquemiller, *Biochemistry*, 2006, **45**, 2721; (*b*) V. L. Gein, N. A. Rassudikhina, N. V. Shepelina, M. I. Vakhrin, E. B. Babushkina and E. V. Voronina, *Pharm. Chem. J.*, 2008, **42**, 519; (*c*) X. Li, N. Liu, H. Zhang, S. E. Knudson, R. A. Slayden and P. J. Tonge, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6306; (*d*) M. Hu, J. Fan, H. Li, K. Song, S. Wang, G. Cheng and X. Peng, *Org. Biomol. Chem.*, 2011, **9**, 980; (*e*) S. Bondock, S. Adel, H. A. Etman and F. A. Badria, *Eur. J. Med. Chem.*, 2012, **48**, 192; (*f*) K. Azuma, S. Suzuki, S. Uchiyama, T. Kajiro, T. Santa and K. Imai, *Photochem. Photobiol. Sci.*, 2003, **2**, 443; (*g*) T. Nishio, *J. Chem. Soc., Perkin Trans. 1*, 1990, 565; (*h*) S. Nonell, L. R. Feñrrares, A. Caete, E. Lemp, G. Günther, N. Pizarro and A. L. Zanocco, *J. Org. Chem.*, 2008, **73**, 5371.

15 (*a*) Y. M. Lee and Y. S. Park, *Heterocycles*, 2009, **78**, 2233; (*b*) S. Luo and J. K. De Brabander, *Tetrahedron Lett.*, 2015, **56**, 3179; (*c*) R. I. Storer, D. E. Carrera, Y. K. Ni and

D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84; (*d*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.*, 2006, **45**, 6751; (*e*) F. Shi, W. Tan, H.-H. Zhang, M. Li, Q. Ye, G.-H. Ma, S.-J. Tu and G.-G. Li, *Adv. Synth. Catal.*, 2013, **355**, 3715; (*f*) A. V. Maikov, K. Vrankova, S. Stoncius and P. Kocovsky, *J. Org. Chem.*, 2009, **74**, 5839; (*g*) X.-Z. Peng, W.-C. Yuan and X.-M. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2132; (*h*) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (*i*) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 2442; (*j*) L.-Q. Lu, Y.-H. Li, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 2763; (*k*) J. L. Núñez-Rico and A. Vidal-Ferran, *Org. Lett.*, 2013, **15**, 2066.

16 (*a*) C. Trebaul, J. Roncali, F. Garnier and R. Guglielmetti, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2657; (*b*) R. B. Moffet, *J. Med. Chem.*, 1966, **9**, 475; (*c*) A. Chilin, A. Confente, G. Pastorini and A. Guiotto, *Eur. J. Org. Chem.*, 2002, 1937; (*d*) D. N. Nicolaides, D. R. Gautam, K. E. Litinas, D. J. Hadjipavlou-Litina and C. A. Kontogiorgis, *J. Heterocycl. Chem.*, 2004, **41**, 605; (*e*) D. N. Nicolaides, R. W. Awad and E. A. Varella, *J. Heterocycl. Chem.*, 1996, **33**, 633; (*f*) I. Yavari, S. Souri, M. Sirouspour and H. Djahaniani, *Synthesis*, 2006, 3243; (*g*) N. Zidar and D. Kikelj, *Tetrahedron*, 2008, **64**, 5756; (*h*) R. Ballini, A. Palmieri, M. A. Talaq and S. Gabrielli, *Adv. Synth. Catal.*, 2009, **351**, 2611.

17 R. Ballini, A. Palmieri, M. A. Talaq and S. Gabrielli, *Adv. Synth. Catal.*, 2009, **351**, 2611.

18 S. Gräßle, S. Vanderheiden, P. Hodapp, B. Bulat, M. Nieger, N. Jung and S. Bräse, *Org. Lett.*, 2016, **18**, 3598.

19 S. Yan, L. Ye, M. Liu, J. Chen, J. Ding, W. Gao, X. Huang and H. Wu, *RSC Adv.*, 2014, **4**, 16705.

20 (*a*) L.-Q. Lu, Y. Li, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 2763; (*b*) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 2442; (*c*) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (*d*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.*, 2006, **45**, 6751.

21 T. Kano, R. Takechi, R. Kobayashi and K. Maruoka, *Org. Biomol. Chem.*, 2014, **12**, 724.

22 C. Huo, J. Dong, Y. Su, J. Tang and F. Chen, *Chem. Commun.*, 2016, **52**, 13341.

23 (*a*) R. P. Pandit, S. H. Kim and Y. R. Lee, *Adv. Synth. Catal.*, 2016, **358**, 3586; (*b*) R. P. Pandit, S. H. Kim and Y. R. Lee, *Org. Biomol. Chem.*, 2016, **14**, 6996; (*c*) R. P. Pandit and Y. R. Lee, *Adv. Synth. Catal.*, 2015, **357**, 2657; (*d*) R. P. Pandit, K. Sharma and Y. R. Lee, *Synthesis*, 2015, **47**, 3881; (*e*) R. P. Pandit and Y. R. Lee, *RSC Adv.*, 2013, **3**, 22039.

24 (*a*) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234; (*b*) S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, **48**, 1756.

25 P.-L. Shao, J.-Y. Liao, Y. A. Ho and Y. Zhao, *Angew. Chem. Int. Ed.*, 2014, **53**, 5435.

26 (*a*) Y. Wu, X. Peng, B. Luo, F. Wu, B. Liu, F. Song, P. Huang and S. Wen, *Org. Biomol. Chem.*, 2014, **12**, 9777; (*b*) R. R. Singh and R.-S. Liu, *Chem. Commun.*, 2017, **53**, 4593; (*c*) F. Damkaci, A. Alawaed and E. Vik, *Tetrahedron Lett.*, 2016, **57**, 2197.