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Palladium-catalyzed selective *ortho* C–H alkoxylation at 4-aryl of 1, 4-disubstituted 1, 2, 3-triazoles

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ABSTRACT

The *ortho*- C–H bonds at C(4)-aryl of 1, 4-disubstituted 1, 2, 3-triazoles were regioselectively alkoxylated in good to excellent yields with under the directing of the triazole ring. Some products were found to exhibit strong antifungal capacity to fight against root-rot disease of *Panax notoginseng* by testing the minimum inhibitory concentration (MIC).

1. Introduction

Since the Huisgen 1, 3-dipolar cycloaddition of azides and alkynes was developed into the “click chemistry” by Sharpless at the beginning of this century [1], the 1, 2, 3-triazole derivatives have been widely employed in various fields such as organic synthesis [2], materials science [3], medicinal chemistry [4], biological technology [5], and agricultural area [6]. These extensive applications and current new emerging problems have vigorously promoted the explorations for constructions of new type of 1, 2, 3-triazoles, especially by means of direct C–H functionalization process. In the past few years, Kuang group has mainly modified 2-monosubstituted 1, 2, 3-triazoles through C–H activation [7]. Meanwhile, great efforts have been recently devoted to the regioselective modification of 1, 4-disubstituted 1, 2, 3-triazoles, which are more challenging owing to the plenty C–H bonds available from different region [N(1)-aryl, C(4)-aryl, and C(5)-H]. Ackermann and Chen groups have demonstrated Pd-catalyzed regioselective arylation and alkenylation of C–H bonds on C(5) position of the triazole ring respectively (Scheme 1a) [8]. The *ortho*- C–H bond on N(1)-aryl can also be functionalized through Ru-catalyzed alkenylation and arylation processes [9] (Scheme 1b). While efforts were also paid to the modification of *ortho*- C–H on C(4)-aryl of 1, 4-diaryl 1, 2, 3-triazoles including *mono*- C–H functionalizations (nitration halogenation, acylation, and acyloxylation) [10] and *di*-C–H transformations (arylation and alkenylation) with the use of Pd, Ru or Rh as a catalyst (Scheme 1c) [11]. Recently, triazole-assisted C–H formylation, alkylation and alkoxycarbonylation were also demonstrated [12]. Despite these remarkable advances, a general method for direct *ortho*- C–H alkoxylation of 1, 4-disubstituted 1, 2, 3- triazoles unfortunately proved elusive.

Herein, we would like to report an efficient protocol for direct *ortho*- C–H alkoxylation of 1, 4-disubstituted 1, 2, 3-triazoles using alcohol as the alkoxyl source. Moreover, the alkoxylated products obtained have been demonstrated to exhibit strong antifungal capacity to fight against root-rot disease of *Panax notoginseng*, a traditional Chinese medicine material (Scheme 1d).

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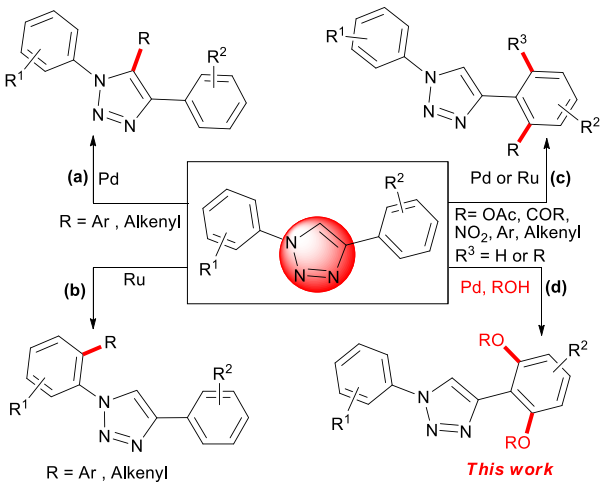


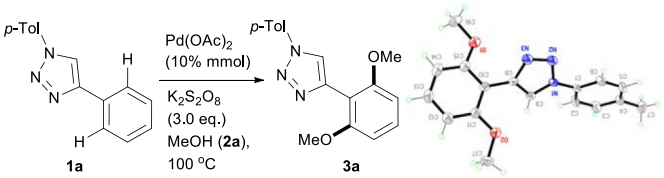
Scheme 1. Triazole-directed C–H activation of 1, 4-diaryl 1,2,3-triazoles.

2. Results and discussion

We initiated our investigation by treating 4-phenyl-1-(*p*-tolyl)-1*H*-1, 2, 3-triazole **1a** (0.3 mmol) and methanol **2a** (12 mmol) as both reactant and solvent with Pd catalyst at 100 °C (Table 1). The effects of catalyst, oxidant, temperature, and the amount of MeOH were explored respectively. We were delighted to find that the desired product **3a** was obtained in 83% yield in the presence of 10 mmol % $Pd(OAc)_2$ as the catalyst, 3.0 equiv of $K_2S_2O_8$ as the oxidant, and 40 equiv MeOH as both the methoxyl source and solvent for 12 h (Table 1, entry 1). The molecular structure of product **3a** was unambiguously confirmed by a X-ray study (CCDC: 1814595). Not surprisingly, the reaction did not occur in absence of catalyst or oxidant (Table 1, entries 2–3). Inferior performance was also observed when other Pd such as $PdCl_2$ and $Pd_2(dba)_3$, or other oxidants including $(NH_4)_2S_2O_8$ and TBHP were used instead (Table 1, entries 4–7). Next, the amount of $Pd(OAc)_2$ was examined, and it turned out that the efficiency was affected upon reducing the loading of $Pd(OAc)_2$ (Table 1, entry 8). Subsequently, the amount of $K_2S_2O_8$ was examined and changing the amount of $K_2S_2O_8$ to 2 or 4 equiv. Both led to a reduction of the yield (Table 1, entries 9–10). The amount of MeOH is another factor that affects the conversion. More MeOH like 50 equivalent used had no obvious contribution to the product while 30 equivalents of MeOH generated a much lower yield (Table 1, entries 11–12). Raising or decreasing the reaction temperature also affected the methoxylation process remarkably (Table 1, entries 13–15).

With the optimal conditions in hand (Table 1, entry 1), we firstly examined the scope of 1, 4-disubstituted 1, 2, 3-triazoles. The reactions of methanol **2a** with various 1, 4-disubstituted 1, 2, 3-triazoles **1** proceeded smoothly to generate the desired products **3** in good to excellent yields (Table 2, **3a**-**3t**). The 1, 2, 3-triazoles that have CH_3, OH, or Br at *meta*- or *para*-position of the N(1)-aryl produced higher yields in comparison with those containing the substituents at *ortho*-position (Table 2, **3a** and **3d** vs. **3c**; **3j** vs.

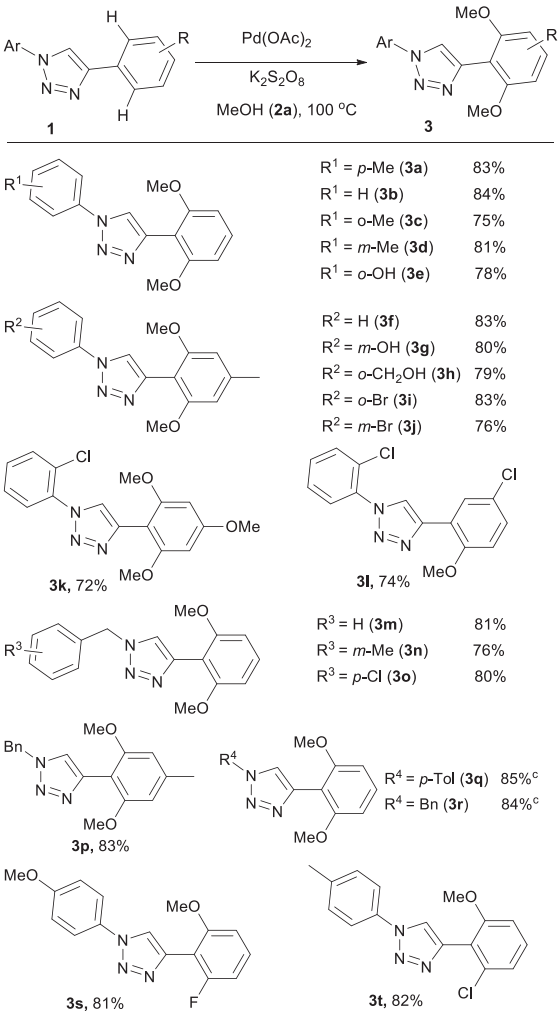
Table 1
Optimization of the reaction conditions[a].



Entry	Conditions changed	Yield(%)[b]
1	–	83
2	no $Pd(OAc)_2$	0
3	no $K_2S_2O_8$	0
4	$PdCl_2$ instead of $Pd(OAc)_2$	45
5	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	23
6	$(NH_4)_2S_2O_8$ instead of $K_2S_2O_8$	34
7	TBHP instead of $K_2S_2O_8$	0
8	5 mol % $Pd(OAc)_2$	35
9	2.0 equiv $K_2S_2O_8$	52
10	4.0 equiv $K_2S_2O_8$	74
11	50 equiv MeOH	82
12	30 equiv MeOH	63
13	80 °C	54
14	90 °C	69
15	120 °C	74

[a] Reaction conditions unless noted: 4-phenyl-1-(*p*-tolyl)-1*H*-1, 2, 3-triazole **1a** (0.3 mmol), MeOH **2a** (12 mmol), $Pd(OAc)_2$ (10 mol %), and $K_2S_2O_8$ (0.9 mmol) at 100 °C for 12 h.
[b] Yield of isolated product.

Table 2
Scope of 1, 4-disubstituted 1, 2, 3-triazoles[a,b,c].



[a] Reaction conditions: 1, 4-disubstituted 1, 2, 3-triazoles 1 (0.3 mmol), $Pd(OAc)_2$ (10 mol %) and $K_2S_2O_8$ (0.9 mmol) , MeOH (12 mmol) at 100 °C for 12 h
[b] Yield of isolated product.
[c] Yield from substrate bear an *ortho*-OMe on C(4) aryl.

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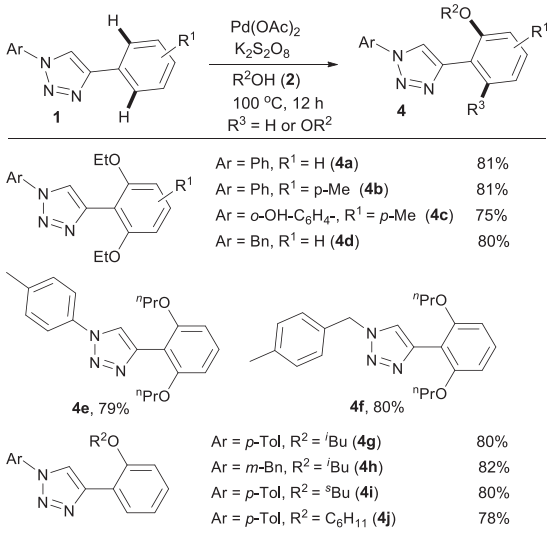
3i). Moreover, the substrates with an electron-donating group (OH, CH_2OH) seem superior to those with electron-withdrawing group (Br) on the N(1)-aryl (Table 2, **3g** and **3h** vs. **3i** and **3j**). Obviously, this process exhibits good tolerance of bromine, phenol hydroxyl, and alcohol hydroxyl. To our delighted, the substrates regardless with an electron-donating or electron-withdrawing substituent on N(4)-aryl could all generate the corresponding products in good yields (Table 2, **3f**-**3k**, **3p**). It is worth noted that *mono*-methoxylated product could be delivered when the substrate contained an *ortho*- or *meta*-substituent on the C(4)-aryl (Table 2, **3l**, **3q**-**3t**). And substituent on C(4)-aryl seems no obvious affections on the yield. Additionally, 1-benzyl 1, 2, 3-triazoles were also suitable for this system and could all generate the expected products in good yields (Table 2, **3m**-**3p**).

We next turned our attention to explore the scope of alcohols (Table 3). A variety of 1, 4-disubstituted 1, 2, 3-triazoles could be coupled with primary and secondary alcohols smoothly, and for most cases the alkoxylated products were obtained in good yields (Table 3, **4a**-**4j**). For primary alcohols such as ethanol and ^{n}PrOH, the corresponding dialkoxylated molecule could selectively acquired and no *mono*-methoxylated product were observed (Table 3, **4a**-**4f**). While bulkier alcohols including ^{i}BuOH, ^{s}BuOH, and cyclohexanol specifically delivered *mono*-alkoxylated molecule in good yields (Table 3, **4g**-**4j**).

To expand the applications of the method and prove the directing role of the 1, 2, 3-triazole ring, we investigated some other substrates **5** (Table 4). When using 2-pyridyl as the directing group, the dimethoxylated product **6a** from 2-phenylpyridine **5a** was obtained with an excellent of 91% (Tables 4 and **6a**). As to 1-phenylpyrazole **5b**, the methoxylation process could also go smoothly with 65% yield (Tables 4 and **6b**). For substrate of 1, 1′-biphenyl **5c** without a directing group, the corresponding alkoxylated product was not detected, which means that the triazole-ring was supposed to act as a directing group in the alkoxylation process (Tables 4 and **6c**).

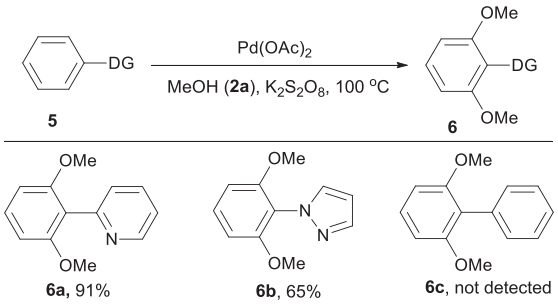
In our searching for fungicides, the antifungal activities of the products were evaluated by microbroth dilution technique (Table 5) [13], toward the three fungal strains including

Table 3
Scope of alcohols[a,b].



[a] Reaction conditions: Reaction conditions: 1, 4-disubstituted 1, 2, 3-triazoles **1** (0.3 mmol), alcohols **2** (12 mmol), $Pd(OAc)_2$ (10 mol %), and $K_2S_2O_8$ (0.9 mmol) at 100 °C for 12 h.
[b] Yield of isolated product.

Table 4
Scope of other substrates[a,b].



[a] **5** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), MeOH (12 mmol), and $K_2S_2O_8$ (0.9 mmol) at 100 °C for 12 h.
[b] Yield of isolated product.

F. oxysporum, *F. solani*, and *C. destrutans* which are mainly accompanied with root-rot disease of *Panax notoginseng*, a traditional Chinese medicinal material with high-valued functions of activating blood circulation and alleviating pain with great medicinal and economic significance [14]. As a result, compounds **3a**, **3b**, **3f**, and **4i** exhibited excellent inhibitory activities toward all the strains and showed higher antifungal activities compared to commercial agricultural chemical of *Propamocarb*. Additionally, compounds **3c** and **3p** have good inhibitory effect on *F. oxysporum* and *F. solani*. Compounds **3s** and **3t** could inhibit *F. oxysporum* and *C. destrutans* growth efficiently. It should be noted that product 3**b** possesses amazing activity against *F. solani* (MIC value: 9.4 ± 0.0 μg/mL) and is more competent compared to commercial agricultural chemicals like *Flutriafol*, *Grondverbeteraar*, *Hymexazol* and *Propamocarb*.

To obtain further insight into the reaction mechanisms, we have carried out the kinetic isotope effect experiments between 4-phenyl-1-(*p*-tolyl)-1*H*-1, 2, 3-triazole **1a** and **1a**-$\boldsymbol{d_5}$. This intermolecular kinetic isotope effect (KIE) study showed that the k_H/k_D of **3a** to **3a**-$\boldsymbol{d_3}$ was determined to be 4.88, indicating that the C–H bond cleavage should be involved in the rate-limiting step (Scheme 2).

Based on our studies and previous reports [7b,11d,15], we proposed a possible Pd(II)/Pd(IV) mechanism for this *ortho*- C–H

Table 5
The MIC values (μg/mL) of the compounds.

Product	*F. oxysporum*	*F. solani*	*C. destructans*
3a	75 ± 0.0	75 ± 0.0	113 ± 21.0
3b	113 ± 21.7	9.4 ± 0.0	120 ± 18.4
3c	105 ± 18.4	49.8 ± 12.6	>150
3f	45 ± 7.5	28.1 ± 5.4	105 ± 18.4
3h	>150	>150	>150
3j	>150	75 ± 0.0	>150
3n	>150	>150	>150
3o	>150	>150	>150
3p	150 ± 0.0	56.3 ± 10.8	>150
3m	>150	>150	>150
3s	150 ± 0.0	>150	51.6 ± 14.1
3t	150 ± 0.0	>150	46.7 ± 9.4
4d	>150	>150	>150
4f	>150	>150	>150
4g	>150	>150	>150
4h	>150	>150	>150
4j	>150	>150	150 ± 0.0
4i	47 ± 9.0	26.3 ± 4.6	100 ± 25.0
Hymexazol[a]	50 ± 13.0	12.5 ± 3.1	12.5 ± 3.1
Flutriafol[a]	37.5 ± 0.0	135 ± 15.0	3.8 ± 0.6
Grondverbeteraar[a]	>150	>150	75 ± 0.0
Propamocarb[a]	150 ± 0.0	>150	150 ± 0.0

[a] A positive control.

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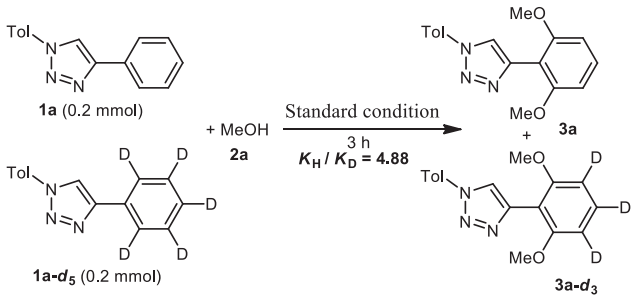
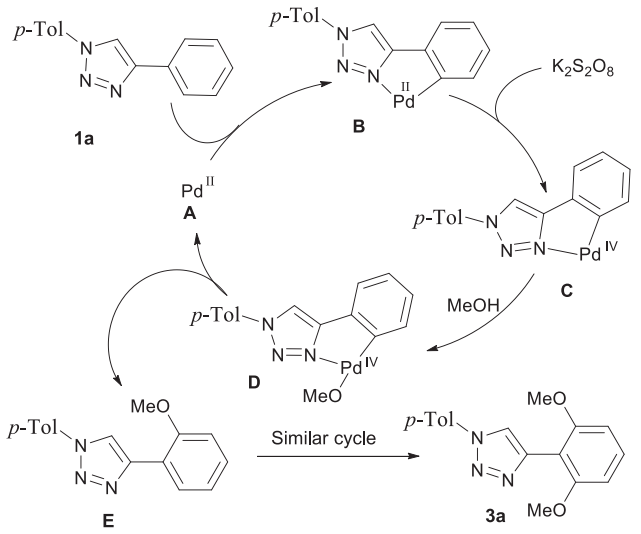


Scheme 2. KIE study.



Scheme 3. Possible Mechanism.

alkoxylation on C(4)-aryl of 1, 4-disubstituted 1, 2, 3-triazoles (Scheme 3). Firstly, selective coordination of electron-richer N(3) in 1, 2, 3-triazole **1a** to the Pd(II) species **A** combined with C–H activation forms a five-membered palladacycle **B** [16]. Next, the Pd(II) intermediate **B** was oxidized to Pd(IV) intermediate **C** by $K_2S_2O_8$ and followed by ligand exchange with methanol **2a** to form **D**. Subsequently, the intermediate **D** underwent a reductive elimination process, regenerating Pd(II) and producing the *mono*-alkoxylation intermediate **E**, which then might transform to dialkoxylated product **3a** by another similar catalytic cycle.

3. Conclusion

We have developed a $Pd(OAc)_2$ catalyzed regioselective and efficient method for the directed C–H alkoxylation on C(4)-aryl of 1, 4-disubstituted 1, 2, 3-triazoles using alcohols as alkoxylating reagents. Directed by N(3) of 1, 2, 3-triazole ring, *di*- or *mono*-alkoxylation process can be facilely achieved and various etherified 1, 4-disubstituted 1, 2, 3-triazole derivatives were obtained in good to excellent yields. Antifungal evaluation discloses that products **3a**, **3b**, **3f** and **4i** possess a broad spectrum of antifungal properties against the three agricultural pathogenic fungi of *F. oxysporum*, *F. solani*, and *C. destrutans*, indicating its potential for developing into the antifungal agents for the treatment of root-rot disease of *Panax notoginseng*. Some molecules showed higher potency than commercial products.

4. Experimental

4.1. General information

^1H and ^{13}C NMR spectra were recorded with a Bruker ACF spectrometer (400 MHz, 500 MHz and 600 MHz) in $CDCl_3$ with TMS as an internal standard. All reactions were monitored by TLC with HuanghaiGF 254 silica gel coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure. Infrared spectra were taken on a Bruker Vertex Series FTIR (KBr) and are reported in reciprocal centimeters (cm^{-1}). Melting points were obtained using a Büchi melting point apparatus and are uncorrected. HRMS spectra were recorded on Waters Micromass Premier Q-TOF spectrometer. Determination of minimum inhibitory concentrations (MIC) were carried out in 96-well plates and the absorbance of each well was measured at 595 nm by using microplate reader (Thermo. Model:1510).

4.2. General procedure for the target products *3*, *4*, and *6*

1, 4-Disubstituted 1, 2, 3-triazole **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), alcohol **2** (12 mmol), and $K_2S_2O_8$ (0.9 mmol) were sequentially added to a 15 mL pressure tube. The tube was sealed, and the resulting mixture was stirred at 100 °C for 12 h. After consumption of the 1, 4-disubstitued 1, 2, 3-triazole monitored by TLC analysis, the mixture was diluted with EtOAc (50 mL) and filtered. The combined organic layers were washed with brine (3 × 5 mL) and dried with Na_2SO_4. After filtration, the mixture was concentrated under reduced pressure to afford the crude product. Purification by column chromatography on silica gel [EtOAc/petroleum ether (PE), 1:4] afforded the desired product **3** and **4**. And the procedure for the target molecule of **6** is similar to **3** and **4**.

4.3. General procedures for intermolecular kinetic isotope effect

4-Phenyl-1-(*p*-tolyl)-1*H*-1, 2, 3-triazole (**1a**) (47 mg, 0.2 mmol), d_5-4-phenyl-1-(*p*-tolyl)-1*H*-1, 2, 3-triazole (**1a-*d*$_5$**) (48 mg, 0.2 mmol), $Pd(OAc)_2$ (8.5 mg, 0.04 mmol), MeOH (16 mmol) and $K_2S_2O_8$ (324 mg, 1.2 mmol) were sequentially added to a 15 mL pressure tube. The tube was sealed, and the resulting mixture was stirred at 100 °C for 3 h. The mixture was diluted with EtOAc (50 mL) and filtered. The combined organic layers were washed with brine (3 × 5 mL) and dried with Na_2SO_4. After filtration, the mixture was concentrated under reduced pressure to afford the crude product. Purification by column chromatography on silica gel [EtOAc/petroleum ether (PE), 1:4] afforded the desired product **3a** and **3a-*d*$_3$**. The ratio of **3a**/(**3a-*d*$_3$**) was determined to be 0.83/0.17 ($k_H/k_D = 4.88$) by ^1H NMR spectroscopy.

4.4. Determination of minimum inhibitory concentrations (MIC)

The concentrations of conidial suspensions were adjusted to be 1 × 104 spores/mL for each fungus in a 1/4 liquid PDA growth medium. Each compound was dissolved in DMSO with the initial concentration of 6 mg/mL. A mixture formed from 4 μL samples and 156 μL conidial suspensions in the first row of a 96-cell microtiter plate, and then diluted two-fold with the same solution to adjust the concentration to 150–0.29 μg/mL. Hymexazol, flutriafol, grondverbeteraar and propamocarb were used as positive controls. The plates, securely sealed with a polyester sealing film (VWR) were incubated in a fungal incubator at 28 °C for 36 h, and the absorbance of each well was measured at 595 nm by an enzyme-labeled instrument. The MIC was defined as the lowest concentration of the compound producing complete inhibition of visible growth.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.130985.

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