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Synthesis of 3',4'-Diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']-oxadiazol]-2-ones *via* DMAP-catalyzed Domino Reactions and Their Antibacterial Activity

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A convenient and metal-free DMAP-catalyzed domino reaction of isatins, arylamines and hydroximoyl chlorides has been developed to achieve 1,3-dipolar cycloaddition of imines into aryl nitrile oxides at ambient temperature. In this one-pot transformation, a 1,2,4-oxadiazole skeleton was efficiently formed. This methodology needs no extra additives and features wide substrate scope, good functional group tolerance and mild reaction conditions. A plausible mechanism for this process was proposed. Moreover, the antibacterial activities of the products were evaluated towards *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* using the Broth microdilution method.

Keywords 4-dimethylaminopyridine, antimicrobial activity, isatins, domino reactions, oxadiazoles

Introduction

Nitrogen-containing heterocycles were commonly used as scaffolds on pharmacophores which could be arranged to produce potent and selective drugs.[1] Within the drug discovery and development industry, the 1,2,4-oxadiazole ring system has been proven to be a privileged scaffold. The oxadiazole rings were an essential part of the pharmacophore for several drugs and formed the lead molecules for drugs which were used to treat a variety of diseases including diabetes, obesity, inflammation, cancer and infection.[2] Many compounds which contained the 1,2,4-oxadiazole motif exhibited biological activities including anticancer activity,[3] antiretroviral activity,[4] voltage-gated sodium activity,[5] and the inhibition of acetyl-CoA carboxylase.[6] Because of their medical application, significant efforts have been focused on developing a general synthetic route to access those compounds.[7] Therefore, more general and ecofriendly procedures to synthesize 1,2,4-oxadiazoles from readily available starting materials are desirable.

Organocatalysis has been widely applied in organic synthesis for the new carbon-carbon/heteroatom bond formation. Recently, 4-dimethylaminopyridine (DMAP) and its analogs have been widely used as catalysts in many organic synthesis reactions. Some example reactions include acylation reactions,[8] aldol reactions,[9] [4+2] cycloaddition,[10] Diels-Alder reaction,[11] domino/cascade reaction,[12] multicomponent reantion[13] and others were reported.[14] This study aimed to develop an efficient organic synthesis with DMAP. Previously, we presented an efficient synthesis approach for benzofurans and naphthofurans *via* DMAP-catalyzed cascade reactions.[15] As a part of our ongoing efforts to determine the organo-catalyzed multicomponent reactions,[16] we reported the simplified synthesis of 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones using the DMAP-catalyzed domino reaction of isatins, arylamines and hydroximoyl chlorides in EtOH at an ambient temperature (Scheme 1). In addition, assessment results againsted *S. epidermidis*, *E. coli*, *S. aureus* and *K. pneumonia* indicated that some compounds exhibited significant antibacterial activity, specifically for the multi-drug resistant strain, *Staphylococcus aureus*. This work provided unusual leads for further optimization during the drug discovery process.

Results and Discussion

Initially, isatin (**1a**), *p*-toluidine (**2b**) and *N*-hydroxybenzimidoyl chloride (**3a**) were chosen as the starting materials in the model reaction to optimize the reaction conditions, and the results were presented in Table 1. When the reaction was carried out with ethanol by using

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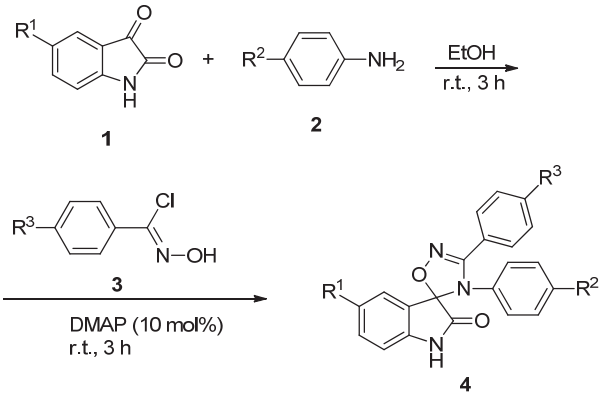
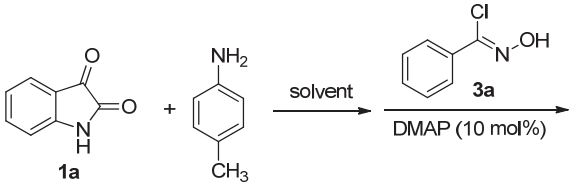
Scheme 1 Synthesis of 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones *via* the DMAP-catalyzed domino reaction of isatins, arylamines, and hydroximoyl chlorides

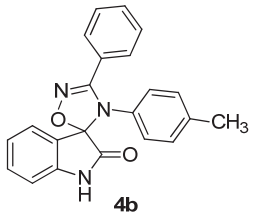


DMAP as the catalyst, a higher yield of the desired product was obtained (Table 1, Entry 9). In a control experiment, only a small amount of the desired product was detected by TLC in the absence of DMAP (Table 1, Entry 22). Here, the yield was not improved by increasing the amount of catalyst (Table 1, Entry 24). Although, it also had good yield (85%) by decreasing the amount of catalyst to 5 mol%, more by-products were produced and the desired product was difficult to separate and purify. Other solvents including CH_2Cl_2, tetrahydrofuran (THF), Et_2O, dimethylformamide (DMF), acetonitrile, toluene, methanol (MeOH) and H_2O did not provide satisfactory results (Table 1, Entries 1—8). Different catalysts were also tested (Table 1, Entries 10—16). The use of other organic bases including pyridine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), triethylamine (TEA), and imidazole provided inferior results (Table 1, Entries 10—13). Replacing the organic bases with other inorganic bases including $KHCO_3$, K_2CO_3, and KOH decreased the reaction yields (Table 1, Entries 14—16). The effects of temperature and reaction time were also investigated (Table 1, Entries 17—21). It was found that increasing of the reaction temperature/time did not improve the yield. Therefore, the optimum reaction conditions, giving an 88% yield of the product, were 10 mol % DMAP, 6 h reaction time, and ambient temperature.

After the optimal conditions were determined, the scope of this domino reaction was investigated (Table 2). As summarized, a wide variety of isatin (**1**), arylamine (**2**) and hydroximoyl chloride (**3**) analogs were tolerated, and the resulting product yields were good to excellent. For the isatins, substrates with electron-withdrawing groups (F, Cl, Br, I) generally resulted in higher yields (Table 2, Entries 3—6) than substrates with electron-donating groups (CH_3, CH_2CH_3) (Table 2, Entries 7, 8). For the different arylamines (**2**), substrates with a strong electron-donating group (OCH_3) resulted in one of the highest reported yields (Table 2, Entry 15). Among the hydroximoyl chlorides (**3**) that were examined, substrates bearing a strong electron-donating group (OCH_3, OCH_2CH_3, $N(CH_3)_2$) or a strong electron-withdrawing group (NO_2) lead to lower yields (Table 2, Entries 12, 13, 18, 19). The chemical structure of compound **4b** was unequivocally confirmed by single-crystal X-ray analysis as shown in Figure 1.[17]

Table 1 Optimization of reaction conditions[a]





Entry	Base	Solvent	*T*/℃	Time/h	Yield[b]/%
1	DMAP	CH_2Cl_2	r.t.	6	75
2	DMAP	THF	r.t.	6	78
3	DMAP	Et_2O	r.t.	6	69
4	DMAP	DMF	r.t.	6	82
5	DMAP	CH_3CN	r.t.	6	60
6	DMAP	Toluene	r.t.	6	64
7	DMAP	MeOH	r.t.	6	77
8	DMAP	H_2O	r.t.	6	51
9	DMAP	EtOH	r.t.	6	88
10	Pyridine	EtOH	r.t.	6	80
11	DBU	EtOH	r.t.	6	49
12	Et_3N	EtOH	r.t.	6	78
13	Imidazole	EtOH	r.t.	6	52
14	$KHCO_3$	EtOH	r.t.	6	57
15	K_2CO_3	EtOH	r.t.	6	60
16	KOH	EtOH	r.t.	6	51
17	DMAP	EtOH	40	6	85
18	DMAP	EtOH	60	6	82
19	DMAP	EtOH	80	6	80
20	DMAP	EtOH	r.t.	3	62
21	DMAP	EtOH	r.t.	12	84
22	—	EtOH	r.t.	6	Trace
23[c]	DMAP	EtOH	r.t.	6	85
24[d]	DMAP	EtOH	r.t.	6	87

[a] Reaction conditions: isatin (**1a**) (0.3 mmol), *p*-toluidine (**2b**) (0.3 mmol), *N*-hydroxybenzimidoyl chloride (**3a**) (0.3 mmol), base (0.03 mmol), and EtOH (5 mL). [b] Isolated yield. [c] 5 mol% catalyst was used. [d] 20 mol% catalyst was used.

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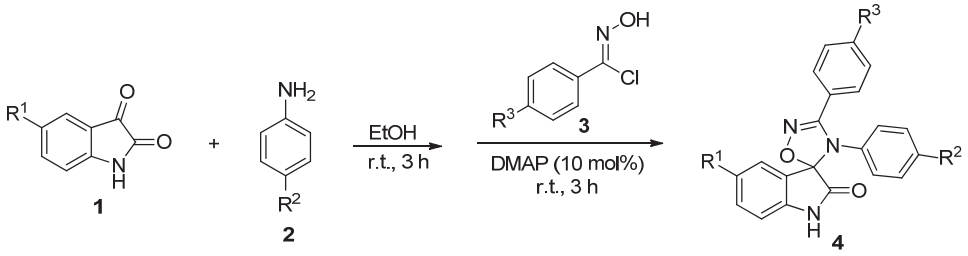
Table 2 Synthesis of 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones (**4**) *via* DMAP-catalyzed domino reactions[a]



Entry	R^1	R^2	R^3	Product	Yield[b]/%
1	H (**1a**)	H (**2a**)	H (**3a**)	**4a**	83
2	H (**1a**)	CH_3 (**2b**)	H (**3a**)	**4b**	88
3	F (**1b**)	CH_3 (**2b**)	H (**3a**)	**4c**	85
4	Cl (**1c**)	CH_3 (**2b**)	H (**3a**)	**4d**	89
5	Br (**1d**)	CH_3 (**2b**)	H (**3a**)	**4e**	88
6	I (**1e**)	CH_3 (**2b**)	H (**3a**)	**4f**	90
7	CH_3 (**1f**)	CH_3 (**2b**)	H (**3a**)	**4g**	86
8	CH_3CH_2 (**1g**)	CH_3 (**2b**)	H (**3a**)	**4h**	81
9	H (**1a**)	CH_3 (**2b**)	F (**3b**)	**4i**	94
10	Cl (**1c**)	CH_3 (**2b**)	F (**3b**)	**4j**	95
11	Cl (**1c**)	CH_3 (**2b**)	Br (**3c**)	**4k**	87
12	H (**1a**)	CH_3 (**2b**)	NO_2 (**3d**)	**4l**	78
13	F (**1b**)	CH_3 (**2b**)	$(CH_3)_2N$ (**3e**)	**4m**	82
14	CH_3 (**1f**)	CH_3 (**2b**)	BnO (**3f**)	**4n**	81
15	CH_3CH_2 (**1g**)	CH_3O (**2c**)	H (**3a**)	**4o**	93
16	Cl (**1c**)	$(CH_3)_2CH$ (**2d**)	BnO (**3f**)	**4p**	80
17	Br (**1d**)	F (**2e**)	Cl (**3g**)	**4q**	80
18	CH_3O (**1h**)	Cl (**2f**)	CH_3O (**3h**)	**4r**	79
19	$(CH_3)_2CH$ (**1i**)	Br (**2g**)	CH_3CH_2O (**3i**)	**4s**	80
20	CH_3O (**1h**)	I (**2h**)	H (**3a**)	**4t**	80
21	Cl (**1c**)	H (**2a**)	CN (**3j**)	**4u**	82
22	I (**1e**)	H (**2a**)	CH_3 (**3k**)	**4v**	88

[a] Reaction conditions: isatin (**1**) (0.3 mmol), arylamine (**2**) (0.3 mmol) and hydroximoyl chlorides (**3**) (0.3 mmol), and DMAP (0.030 mmol) at room temperature in EtOH (5 mL) for 6 h. [b] Isolated yields.

Based on our experimental results,[18-20] a plausible mechanism for the formation of 3',4'-diphenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one was proposed (Scheme 2). First, the condensation between isatin **1a** and arylamine **2a** would form intermediate **A**. Then, the 1,3-dipolar cycloaddition of intermediate **A** with the 1,3-dipole **B**, which was generated in situ from *N*-hydroxybenzimidoyl chloride **3a** and treated with DMAP, formed the desired product **4a**, which is an alkaline compound. Subsequently, the compound **4a** reacted with DMAP • HCl to regenerate the catalyst DMAP.

Some control experiments were then carried out to gain some insight into the mechanism of this reaction (Scheme 3). Terminating the reaction of **1a** with **2b** after the first step of the reaction produced an intermediate **A** in 97% yield (Scheme 3, Eq. (1)). Under the

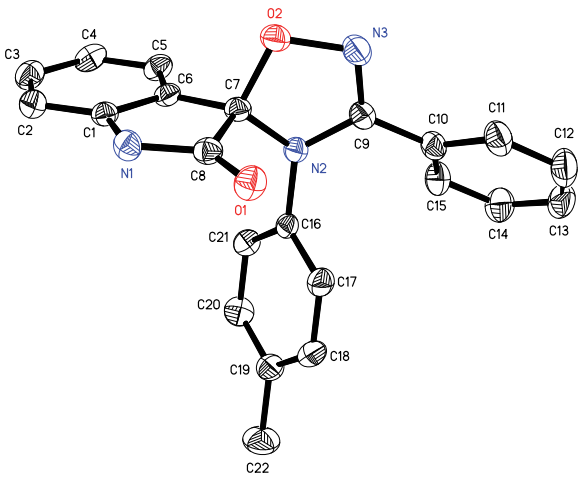
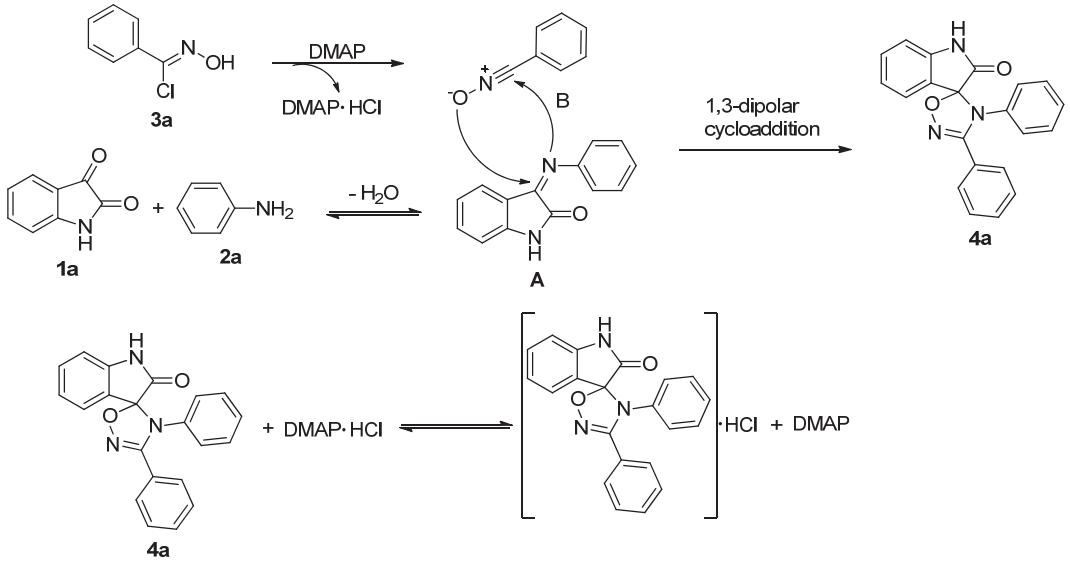


Figure 1 X-ray crystal structure of **4b**.

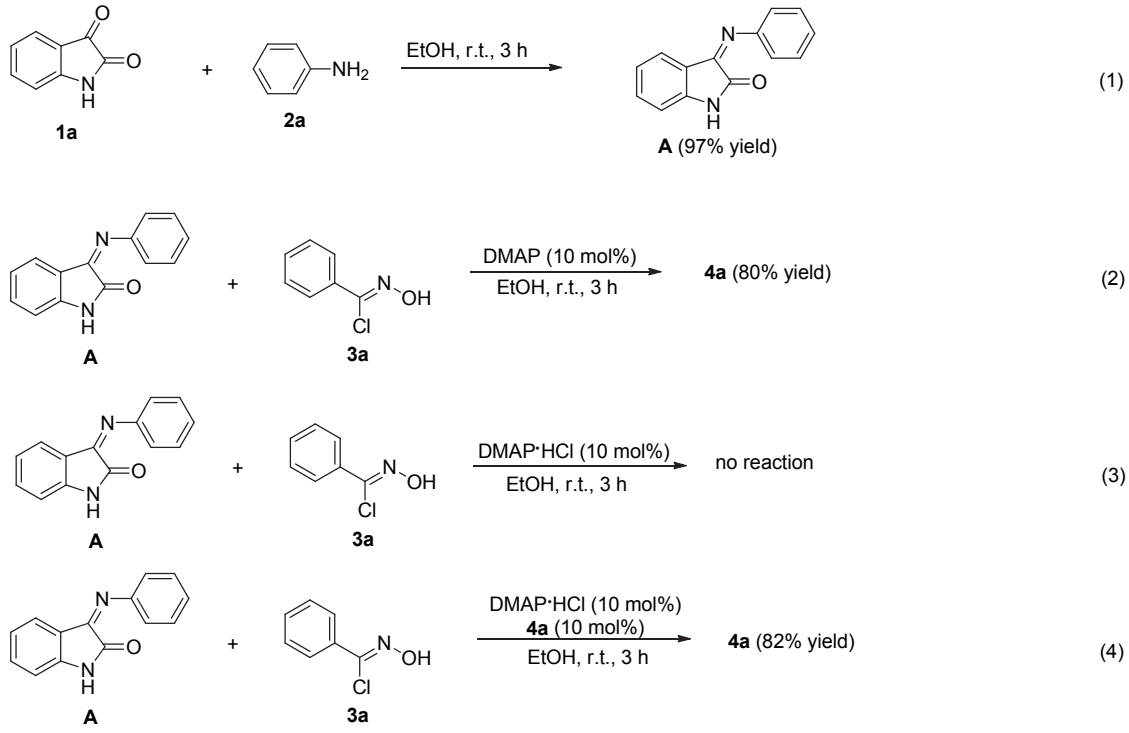
Scheme 2 Proposed mechanism for the formation of 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones (**4**).



reaction conditions in Table 2, the intermediate **A** reacted with *N*-hydroxybenzimidoyl chloride **3a** to give the final product **4a** in 80% yield [Scheme 2, Eq. (2)]. Subsequently, it was found that the reaction of intermediate **A** and **3a** hardly took place when 4-(*N,N*-dimethylamino)pyridine hydrochloride (DMAP•HCl) was used as a catalyst [Scheme 3, Eq. (3)]. In contrast, the reaction was proceeded smoothly, and the desired **4a** was obtained in 82% yield when **4a** (10 mol%) was used as an additive in the reaction system [Scheme 3, Eq. (4)].

In the present study, the antibacterial activities of the synthesized compounds were screened against two gram negative and two gram positive bacterial strains (*S. epidermidis*, *E. coli*, *S. aureus* and *K. pneumonia*) using the Broth microdilution method. The results revealed that some synthesized compounds exhibited antibacterial activity against both *S. epidermidis* and *S. aureus*. The results are summarized in Table 3 and Figure 2. Compared to the standard bacteria against *S. epidermidis*, **4l** showed improved activity. In addition, **4k**, **4j**, **4f** and **4v** exhibited significant antibacterial activity against the *S. aureus* strain which was resistant to most known antibiotics (levofloxacin MIC=32 μg/mL).

Scheme 3 Control experiments



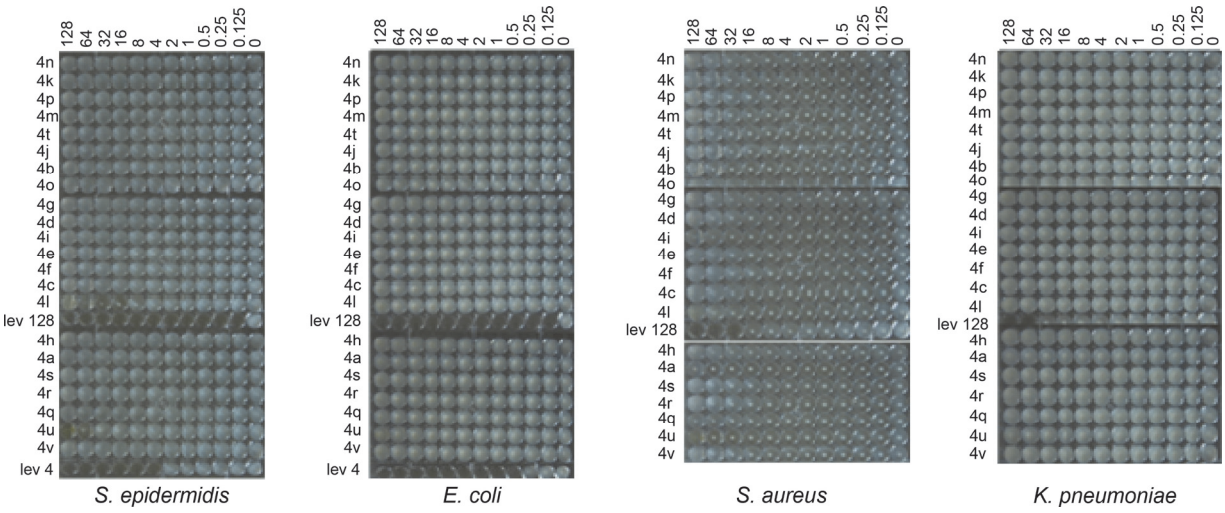


Figure 2 Photos of antibacterial activities with the synthesized compounds.

Table 3 The MIC of all compounds against bacteria (μg/mL)

Compd.	*S. epidermidis*	*E. coli*	*S. aureus*	*K. pneumoniae*
4a	>128	>128	>128	>128
4b	>128	>128	>128	>128
4c	>128	>128	128	>128
4d	>128	>128	128	>128
4e	>128	>128	128	>128
4f	>128	>128	64	>128
4g	>128	>128	128	>128
4h	>128	>128	>128	>128
4i	>128	>128	>128	>128
4j	>128	>128	64	>128
4k	>128	>128	64	>128
4l	64	>128	128	>128
4m	>128	>128	128	>128
4n	>128	>128	>128	>128
4o	>128	>128	>128	>128
4p	>128	>128	128	>128
4q	>128	>128	>128	>128
4r	>128	>128	128	>128
4s	>128	>128	128	>128
4t	>128	>128	128	>128
4u	128	>128	>128	>128
4v	>128	>128	64	>128
levofloxacin	0.125	0.02	32	64

The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. It was the substitutions on indole ring and on the phenyl ring of hydroximoyl chlorides functionality that had distinctive effect on the potency of these compounds against the tested bacterial strains. For instance compound **41**, with 4-NO_2 substituent on the phenyl ring of hydroximoyl chloride was found to be the most active against *S. epidermidis*. Similarly, compounds **4k**, **4j**, **4f** and **4v** with halogen groups (Cl, I) on indole ring were found to have significant antibacterial activity against *S. aureus*. In fact its potency was comparable to standard drug chloramphenicol and ciprofloxacin while far better then ampicillin.[21]

Conclusions

In conclusion, we developed an efficient DMAP-catalyzed domino reaction for the synthesis of 3',4'-diphenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one derivatives. This reaction possessed good to excellent yields from readily available isatins, arylamines and hydroximoyl chlorides. In comparison to the metal-catalyzed reactions, this route is a novel, highly effective, and environment-friendly process. The antibacterial activity of all compounds was also evaluated for both gram negative and gram positive bacteria. Some of the testing compounds inhibited the growth of the *Staphylococcus aureus*, which could potentially solve the problem of multidrug resistance.

Experimental

Chemistry

Unless otherwise specified, all reagents and starting materials were purchased from commercial sources and used as received, and the solvents were purified and dried by standard procedures. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200—300 mesh silica gel with the indicated solvent system according to standard techniques. The ^{1}H and ^{13}C NMR data were recorded on 400 MHz NMR spectrometers, unless otherwise specified. Chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (δ 7.26 for ^{1}H and 76.1 for ^{13}C). Multiplicities are described as s (singlet), d (doublet), t (tri-

plet), q (quartet), or m (multiplet), and coupling constants (*J*) are reported in hertz. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (*m*/*z*) ratios in atomic mass units. IR spectra were measured as dry films (KBr), and peaks are reported in terms of wave number (cm^{-1}).

General procedure for the synthesis of 3',4'-diphenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one derivatives 4

A solution of isatin **1** (1.0 mmol) and arylamine **2** (1.0 mmol) in EtOH (5 mL) was stirred for 3 h at room temperature. When the TLC showed the reactants disappeared, the chloro oxime **3** (1.0 mmol) and DMAP (0.05 mmol) were added, and the reaction continued for another 3 h. Upon completion of the reaction, the mixture was evaporated in a vacuum, extracted by ethyl acetate and a 5% NaOH solution three times, and then washed with brine. Organic layers were combined, dried over Na_2SO_4, filtered, and evaporated in a vacuum. The residue was further purified by flash column chromatography on silica gel (300—400 mesh) with ethyl acetate and petroleum (3∶1, *V*/*V*) as the eluting solvent to give the desired product.

3',4'-Diphenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']-oxadiazol]-2-one (4a) Gray solid. m.p. 221—222 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.63 (s, 1H), 7.57 (d, J=7.6 Hz, 1H), 7.49—7.33 (m, 6H), 7.19—7.04 (m, 4H), 6.86—6.79 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.6, 155.25, 143.2, 136.8, 132.7, 131.2, 129.6, 129.2, 128.4, 127.4, 126.9, 126.8, 124.7, 124.4, 123.3, 111.3, 98.1; IR (KBr) *v*: 3215, 3064, 1731, 1621, 1492, 1387, 1275, 1207, 1141, 843, 751, 690, 587 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{16}N_3O_2$ ($[M+H]^+$) 342.1243, found 342.1238.

3'-Phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4b) Yellow solid. m.p. 187—188 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.50 (s, 1H), 7.58 (d, J=7.2 Hz, 1H), 7.47—7.33 (m, 6H), 7.08 (t, J=7.6 Hz, 1H), 6.98 (d, J=8.0 Hz, 2H), 6.84 (d, J=8.0 Hz, 1H), 6.71 (d, J=8.0 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.7, 155.3, 143.2, 137.0, 134.1, 132.6, 131.1, 130.1, 129.1, 128.4, 127.0, 126.9, 124.7, 124.5, 123.3, 111.3, 98.1, 20.8; IR (KBr) *v*: 2970, 2363, 1736, 1560, 1508, 1473, 1458, 1365, 1229, 1216, 756, 696, 517 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}N_3O_2$ ($[M+H]^+$) 356.1399, found 356.1399.

5-Fluoro-3'-phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4c) White solid. m.p. 113—115 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.61 (s, 1H), 7.60—7.58 (m, 1H), 7.47—7.39 (m, 5H), 7.19 (t, J=8.4 Hz, 1H), 7.01 (d, J=8.4 Hz, 2H), 6.85—6.81 (m, 1H), 6.77 (d, J=8.0 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.9, 157.6 ($^1J_{CF}$=238.4 Hz), 155.3, 139.3 ($^1J_{CF}$=2.9 Hz), 137.2, 133.8, 131.1, 130.2, 129.1, 128.5, 127.3, 126.1 ($^3J_{CF}$=7.4 Hz), 124.5, 119.3 ($^2J_{CF}$=23.7 Hz), 114.7 ($^2J_{CF}$=24.6 Hz), 112.4 ($^3J_{CF}$=7.6 Hz), 98.1, 20.8; IR (KBr) *v*: 2996, 2214, 1732, 1512, 1487, 1418, 1365, 1216, 818, 717, 524 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}FN_3O_2$ ($[M+H]^+$) 374.1305, found 374.1298.

5-Chloro-3'-phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4d) White solid; m.p. 229—231 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.79 (s, 1H), 7.75 (s, 1H), 7.48—7.37 (m, 6H), 7.01 (d, J=8.0 Hz, 2H), 6.87 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.0 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.5, 155.3, 142.0, 137.2, 133.8, 137.2, 132.5, 131.1, 130.2, 129.1, 128.5, 127.3, 127.2, 126.9, 126.5, 124.5, 112.9, 97.9, 20.8; IR (KBr) *v*: 3248, 1752, 1619, 1597, 1511, 1475, 1445, 1389, 1252, 1196, 1149, 1119, 818, 751, 694, 616, 549 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}ClN_3O_2$ ($[M+H]^+$) 390.1009, found 390.1006.

5-Bromo-3'-phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4e) White solid. m.p. 205—207 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.73 (s, 1H), 7.87 (s, 1H), 7.54 (d, J=5.6 Hz, 1H), 7.52—7.39 (m, 5H), 7.02 (d, J=7.6 Hz, 2H), 6.81—7.46 (m, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.3, 155.3, 142.3, 137.2, 135.4, 133.7, 131.1, 130.2, 129.7, 129.1, 128.5, 127.2, 126.9, 124.5, 114.9, 113.4, 97.8, 20.8; IR (KBr) *v*: 2360, 2341, 1749, 1616, 1595, 1575, 1540, 1472, 1418, 1394, 1197, 818, 770, 692, 668, 655 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}BrN_3O_2$ ($[M+H]^+$) 434.0504, found 434.0493.

5-Iodo-3'-phenyl-4'-*p*-tolyl-**4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4f)** White solid. m.p. 245—247 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.74 (s, 1H), 7.97 (s, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.53—7.38 (m, 5H), 7.01 (d, J=8.0 Hz, 2H), 6.75 (d, J=8.0 Hz, 2H), 6.99 (d, J=8.0 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.0, 155.3, 142.8, 141.1, 137.2, 135.1, 133.8, 131.1, 130.2, 129.1, 128.5, 127.1, 127.1, 124.5, 113.7, 97.7, 86.1, 20.8; IR (KBr) *v*: 2363, 1751, 1655, 1615, 1511, 1467, 1389, 1199, 817 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}IN_3O_2$ ($[M+H]^+$) 482.0365, found 482.0356.

5-Methyl-3'-phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4g) White solid. m.p. 116—117 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.44 (s, 1H), 7.45—7.40 (m, 6H), 7.16 (d, J=7.6 Hz, 1H), 6.99 (d, J=8.0 Hz, 2H), 6.73 (t, J=8.4 Hz, 3H), 2.28 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.6, 155.3, 140.6, 136.9, 134.0, 132.9, 132.5, 131.1, 130.1, 129.1, 128.3, 127.2, 127.0, 124.8, 124.7, 111.0, 98.3, 20.8, 20.8; IR (KBr) *v*: 3031, 2970, 2360, 1743, 1648, 1560, 1512, 1493, 1458, 1388, 1289, 1216, 819, 752, 694 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}N_3O_2$ ($[M+H]^+$) 370.1556, found 370.1557.

5-Ethyl-3'-phenyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4h) Gray solid. m.p. 187—188 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.45 (s, 1H), 7.47—7.38 (m, 6H), 7.18 (d, J=7.6 Hz, 1H), 6.98 (d, J=8.4 Hz, 2H), 6.74—6.69 (m, 3H), 2.59—2.54 (m, 2H), 2.15 (s, 3H), 1.15 (t, J=8.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.7, 155.3, 140.9,

139.0, 137.0, 134.2,131.8, 131.1, 130.1, 129.1, 128.4, 127.1, 126.2, 124.8, 124.6, 111.0, 98.3, 28.0, 20.8, 16.3; IR (KBr) *v*: 3242, 2963, 1747, 1626, 1455, 1393, 1205, 819, 752, 694 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}N_3O_2$ ($[M+H]^+$) 384.1712, found 384.1704.

3'-(4-Fluorophenyl)-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4i) White solid. m.p. 211－213 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.56 (s, 1H), 7.59 (d, J=7.2 Hz, 1H), 7.49－7.45 (m, 2H), 7.36 (t, J=7.6 Hz, 1H), 7.28 (t, J=8.8 Hz, 2H), 7.08 (t, J=7.6 Hz, 1H), 6.99 (d, J=8.0 Hz, 2H), 6.84 (d, J=7.6 Hz, 1H), 6.72 (d, J=8.4 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.7, 164.8 ($^1J_{CF}$=247.4 Hz), 154.6, 143.1, 137.1, 133.8, 132.7, 130.9 ($^1J_{CF}$=8.6 Hz), 130.2, 127.1 ($^2J_{CF}$=18.3 Hz), 124.4, 123.3, 121.1 ($^3J_{CF}$=3.4 Hz), 116.5 ($^2J_{CF}$=22.0 Hz), 111.3, 98.1, 20.8; IR (KBr) *v*: 3209, 1728, 1605, 1512, 1470, 1410, 1382, 1239, 1204, 1417, 821, 757,577 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}FN_3O_2$ ($[M+H]^+$) 374.1305, found 374.1294.

5-Chloro-3'-(4-fluorophenyl)-4'-*p*-tolyl-4'*H*-spiro-[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4j) White solid. m.p. 240－241 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.73 (s, 1H), 7.78 (s, 1H), 7.49－7.46 (m, 2H), 7.41－7.39 (m, 1H), 7.25 (t, J=8.8 Hz, 2H), 7.01 (d, J=7.6 Hz, 2H), 6.85 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.5, 164.8, 162.4, 154.5, 141.9, 137.4, 133.6, 132.6, 131.1, 131.0, 130.3, 127.3, 127.3, 126.4, 120.9, 116.4, 116.2, 112.9, 97.9, 20.8; IR (KBr) *v*: 3180, 1749, 1606, 1515, 1477, 1445, 1418, 1393, 1252, 1225, 1194, 1150, 840, 816, 548 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}ClFN_3O_2$ ($[M+H]^+$) 408.0915, found 408.0916.

3'-(4-Bromophenyl)-5-chloro-4'-*p*-tolyl-4'*H*-spiro-[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4k) White solid. m.p. 226－227 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.73 (s, 1H), 7.77 (s, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.40－7.34 (m, 3H), 7.02 (d, J=8.0 Hz, 2H), 6.84 (d, J=8.4 Hz, 1H), 6.75 (d, J=8.0 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.4, 154.7, 141.9, 141.9, 137.5, 133.5, 132.6, 132.2, 130.5, 130.3, 127.4, 127.2, 127.1, 126.3, 124.7, 123.7, 112.9, 98.0, 20.8; IR (KBr) *v*: 3213, 1750, 1621, 1512, 1476, 1402, 1385, 1251, 1196, 1069, 1011, 819, 714, 550 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}BrClN_3O_2$ ($[M+H]^+$) 468.0114, found 468.0108.

3'-(4-Nitrophenyl)-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4l) Yellow solid. m.p. 113－114 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.62 (s, 1H), 8.27 (d, J=8.8 Hz, 2H), 7.68 (d, J=8.4 Hz, 2H), 7.64 (d, J=7.2 Hz, 1H),7.38 (t, J=7.6 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 7.02 (d, J=8.0 Hz, 2H), 6.85 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.4, 154.2, 148.9, 143.2, 137.4, 133.5, 132.9, 130.8, 130.4, 129.7, 127.1, 127.0, 124.4, 124.0, 123.4, 11.4, 98.6, 20.8; IR (KBr) *v*: 3212, 2921, 2851, 2358, 1743, 1620, 1570, 1521, 1471, 1390, 1344, 1201, 1110, 849, 751, 692, 603 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}N_4O_4$ ($[M+H]^+$) 401.1250, found 401.1246.

3'-(4-(Dimethylamino)phenyl)-5-fluoro-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4m) Gray solid. m.p. 132－133 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.55 (s, 1H), 7.47－7.45 (m, 1H), 7.19－7.14 (m, 3H), 7.01 (d, J=8.0 Hz, 2H), 6.83－6.80 (m, 1H), 6.75 (d, J=7.6 Hz, 2H), 6.63 (d, J=8.4 Hz, 2H), 2.91 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.2, 157.5 ($^1J_{CF}$=238.3 Hz), 155.3, 151.7, 139.2 ($^1J_{CF}$=1.4 Hz), 136.9, 134.5, 130.1, 129.4, 127.3, 126.5 ($^3J_{CF}$=7.6 Hz), 119.1 ($^2J_{CF}$=23.9 Hz), 114.4 ($^2J_{CF}$=25.3 Hz), 112.2 ($^3J_{CF}$=8.6 Hz), 111.7, 110.4, 97.7 ($^3J_{CF}$=1.5 Hz), 20.8; IR (KBr) *v*: 2359, 1748, 1610, 1526, 1488, 1387, 1272, 1201, 1180, 818 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}FN_4O_2$ ($[M+H]^+$) 417.1727, found 417.1728.

3'-(4-(Benzyloxy)phenyl)-5-methyl-4'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4n) White solid. m.p. 110－111 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.41 (s, 1H), 7.46－7.32 (m, 8H), 7.14 (d, J=8.0 Hz, 1H), 7.04－6.98 (m, 4H), 6.71 (t, J=7.2 Hz, 3H), 5.11 (s, 2H), 2.27 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.4, 165.1, 159.6, 145.3, 141.7, 141.6, 139.0, 137.5, 137.2, 134.8, 134.7, 133.6, 133.1, 133.0, 131.9, 131.8, 129.7, 121.6, 120.1, 115.7, 102.9, 74.5, 25.6, 25.6; IR (KBr) *v*: 3031, 1746, 1646, 1624, 1540, 1514, 1496, 1380, 1229, 818 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_3$ ($[M+H]^+$) 476.1974, found 476.1971.

5-Ethyl-4'-(4-methoxyphenyl)-3'-phenyl-4'*H*-spiro-[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4o) White solid; m.p. 193－194 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 7.48－7.37 (m, 6H), 7.18 (d, J=7.6 Hz, 1H), 6.82 (d, J=8.8 Hz, 2H), 6.73 (t, J=8.4 Hz, 3H), 3.64 (s, 3H), 2.61－2.56 (m, 2H), 1.17 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.9, 158.4, 155.5, 140.9, 139.0, 131.7, 131.0, 129.3, 129.1, 129.0, 128.4, 126.3, 124.7, 124.7, 114.7, 111.0, 98.4, 55.5, 28.1, 16.3; IR (KBr) *v*: 3180, 2965, 1726, 1626, 1606, 1455, 1511, 1491, 1455, 1393, 1284, 1248, 1211, 1189, 1022, 847, 834, 769, 700, 669 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}N_3O_3$ ($[M+H]^+$) 400.1661, found 400.1651.

3'-(4-(Benzyloxy)phenyl)-5-chloro-4'-(4-isopropyl-phenyl)-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4p) White solid. m.p. 201－202 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.73 (s, 1H), 7.66 (s, 1H), 7.44－7.33 (m, 8H), 7.07 (d, J=8.0 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.0 Hz, 2H), 5.09 (s, 2H), 2.79－2.72 (m, 1H), 1.08 (d, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.6, 160.4, 155.1, 147.7, 141.8, 134.2, 136.8, 132.5, 130.1, 128.8, 128.4, 128.3, 127.5, 127.4, 127.1, 126.8, 126.6, 116.5, 115.3, 112.9, 97.7, 69.7, 33.1, 23.9, 23.8; IR (KBr) *v*: 2355, 1736, 1606, 1513, 1478, 1427, 1388, 1305, 1251, 1203, 1175, 829, 699 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{27}ClN_3O_3$ ($[M+H]^+$) 524.1741, found

524.1736.

5-Bromo-3'-(4-chlorophenyl)-4'-(4-fluorophenyl)-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4q) Yellow solid. m.p. 257—259 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.82 (s, 1H), 7.94 (s, 1H), 7.56—7.43 (m, 5H), 7.13 (t, J=8.4 Hz, 2H), 6.96—6.93 (m, 2H), 6.83 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.1, 159.8 ($^1J_{CF}$=244.4 Hz), 154.5, 142.4, 136.0, 135.6, 132.5, 152.4, 130.4, 129.9 ($^3J_{CF}$=11.8 Hz), 129.7 ($^2J_{CF}$=29.8 Hz), 126.3, 123.1, 116.9 ($^2J_{CF}$=22.6 Hz), 115.0, 113.5, 98.0; IR (KBr) v: 2969, 2231, 1740, 1618, 1594, 1508,1473, 1365, 1216, 1093, 832, 761, 527 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{13}BrClFN_3O_2$ ([M+ H]$^+$) 471.9864, found 471.9851.

4'-(4-Chlorophenyl)-5-methoxy-3'-(4-methoxyphenyl)-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4r) White solid. m.p. 115—117 ℃; ^{1}H NMR (400 MHz, MeOD-d_4) δ: 7.43 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.8 Hz, 3H), 6.96—6.92 (m, 3H), 6.84 (t, J=8.0 Hz, 3H), 3.81 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ: 173.4, 161.8, 156.6, 155.4, 135.5, 135.4, 132.5, 129.7, 128.8, 128.1, 125.3, 117.3, 115.6, 113.9, 112.2, 111.6, 98.4, 54.9, 54.5; IR (KBr) v: 3254, 2836, 2358, 1742, 1608, 1492, 1383, 1256, 1177, 1028, 831, 575 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}ClN_3O_4$ ([M+ H]$^+$) 436.1064, found 436.1058.

4'-(4-Bromophenyl)-3'-(4-ethoxyphenyl)-5-isopropyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4s) White solid. m.p. 91—93 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.55 (s, 1H), 7.37 (t, J=6.8 Hz, 4H), 7.32 (s, 1H), 7.20 (d, J=8.0 Hz, 1H), 6.97 (d, J=8.8 Hz, 2H), 6.81—6.72 (m, 3H), 4.07—4.01 (m, 2H), 2.86—2.79 (m, 1H), 1.37 (t, J=6.8 Hz, 3H), 1.32—1.09 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.7, 160.7, 154.7, 143.7, 141.0, 137.0, 132.4, 130.5, 130.0, 128.8, 124.8, 123.9, 119.9, 116.2, 115.1, 111.0, 97.9, 63.7, 33.3, 24.4, 24.0, 14.9; IR (KBr) v: 3423, 2969, 1739, 1609, 1515, 1489, 1379, 1253, 1216, 1105, 825 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{25}BrN_3O_3$ ([M+H]$^+$) 506.1079, found 506.1070.

4'-(4-Iodophenyl)-5-methoxy-3'-phenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4t) White solid. m.p. 131—133 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.47 (s, 1H), 7.55 (d, J=8.0 Hz, 2H), 7.49—7.47 (m, 1H), 7.44 (s, 4H), 7.19 (s, 1H), 6.95 (d, J=6.8 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.61 (d, J=8.4 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.4, 156.0, 154.9, 138.4, 136.7, 136.2, 131.3, 129.3, 128.8, 128.5, 125.2, 124.3, 118.2, 112.7, 112.2, 98.3, 93.1, 56.1; IR (KBr) v: 3234, 2833, 1742, 1596, 1491, 1380, 1297, 1202, 1027, 820, 769, 749, 697 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}IN_3O_3$ ([M+H]$^+$) 498.0315, found 498.0314.

4-(5-Chloro-2-oxo-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazole]-3'-yl)benzonitrile (4u) White solid. m.p. 99—101 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.82 (s, 1H), 7.91 (d, J=8.4 Hz, 2H), 7.81 (s, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.42—7.39 (m, 1H), 7.25—7.17 (m, 3H), 6.89—6.86 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.1, 154.2, 142.0, 136.0, 133.1, 132.8, 129.9, 129.3, 129.0, 128.0, 127.4, 127.2, 127.0, 126.0, 118.4, 113.7, 113.0, 98.3; IR (KBr) v: 2970, 2360, 2342, 1739, 1594, 1496, 1365, 1228, 1216, 1057, 838, 696, 668, 528 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{14}ClN_4O_2$ ([M+H]$^+$) 401.0805, found 401.0803.

5-Iodo-4'-phenyl-3'-*p*-tolyl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-one (4v) White solid. m.p. 129—131 ℃; ^{1}H NMR (400 MHz, MeOD-d_4) δ: 7.85 (s, 1H), 7.71 (d, J=8.4 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.19—7.16 (m, 5H), 6.87—6.85 (m, 2H), 6.71 (d, J=8.4 Hz, 1H), 4.60 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, MeOD-d_4) δ: 172.7, 156.0, 142.3, 141.4, 140.9, 136.2, 134.8, 129.0, 128.9, 128.0, 127.1, 126.8, 126.7, 120.9, 112.9, 97.8, 84.6, 20.0; IR (KBr) v: 3213, 2357, 1751, 1614, 1594, 1494, 1469, 1384, 1197, 817, 694 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}IN_3O_2$ ([M+H]$^+$) 482.0365, found 482.0360.

Biological assays

The bacterial strain of *Staphylococcus aureus* (Identification number: WXI-004) was obtained from WuXi AppTec (Shanghai) Co., Ltd. Other bacterial strains, such as *Staphylococcus epidermidis* (Identification number: ATCC 35984), *Escherichia coli* (Identification number: ATCC 25922), and *Klebsiella pneumoniae* (Identification number: ATCC BAA-1898), were obtained from American Type Culture Collection (ATCC).

Preparing compound testing plates

Testing compounds were balanced and transferred into 1.5 mL sterile centrifuge tubes. Pure DMSO (Sigma D5879-1L) was used to dissolve the compounds. This stock solution was made and used on the day of testing. On the day of testing, 980μCAMHB (Cation-adjusted Muller Hinton Broth, BD-212322) was added into column 1 of a 96-deep well plate (Corning-3960).

Preparing bacterial inoculum

A day prior to the testing, –80 ℃ bacterial glycerol stocks were streaked onto MHAII (Muller Hinton II Agar, BD-211438) plates. The plates were incubated at 37 ℃ for 20 h. On the day of testing, single colonies were picked from the plate and suspended in 5 mL of sterile saline. A turbidity meter (Siemens MicroScan Turbidity Meter) was used to adjust the turbidity to 0.5 McFarland standard, which is equivalent to a bacterial density of ~1.0×10^8 CFU/mL. The bacteria/saline suspension was diluted another 100× in a CAMHB to 1.0×10^6 CFU/mL. This was used as the inoculum.

Minimum inhibitory concentration (MIC) test

An aliquot of 100 μL bacterial inoculum was transferred into each well of the compound testing plates. Each testing plate was inoculated with a single strain to prevent cross contamination. The final testing concentrations were 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125

and 0 μg/mL. The starting bacterial density was ~5×10^5 CFU/mL. The testing plates were incubated at 37 ℃ for 20 h before the MICs were read.

Determining the MIC

After the 20 h incubation, the MICs were evaluated by visual observation. Based on the CLSI-M7, the MIC is defined as the minimum compound concentration that completely or significantly inhibits the growth of bacterium.

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