Synthesis and Antimicrobial Activities of Oxazepine and Oxazocine Derivatives

Jian Tang[a,b], Yu-liang Jiang[a], Bing-xiang Wang[a,*], and Yong-miao Shen[b,*]

[a] Jiangsu Key Laboratory of Biofunctional Materials, School of Chemistry and Materials Science, Nanjing Normal University, Nanjing 210097, China. E-mail: wangbingxiang@njnu.edu.cn

[b] Department of Chemistry and Chemical Engineering, Shaoxing University, Shaoxing 312000, China. E-mail: shenyongmiao@hotmail.com

* Authors for correspondence and reprint requests

Z. Naturforsch. **69c**, 283 – 290 (2014) / DOI: 10.5560/ZNC.2014-0029
Received February 6 / June 21, 2014 / published online August 13, 2014

A series of annulated 7-membered oxazepine and 8-membered oxazocine derivatives were synthesized by photoreaction of phthalimide derivatives and an alkene. The antimicrobial activities of the synthesized compounds were evaluated, and compounds **18** and **20** exhibited best antibacterial activity against Gram-positive bacteria. The relationships between structure (especially steric structure) and antimicrobial activities are discussed.

Key words: Oxazepine, Oxazocine, Antimicrobial Activity, Structure-Activity Relationship

Introduction

The increasing emergence of bacterial resistance to most antibiotics poses a great threat to health care (Linden, 2002; Medino *et al.*, 2000; Spera and Farber, 1994), and novel therapeutics are needed. Recent research has focused on the development of new antibacterial agents with novel targets.

N,O-containing compounds with medium and large rings are noteworthy synthetic targets because they have a wide range of biological activities (Seto, 2004; Seto and Asano, 2007; Mishra and Panda, 2007; Assoumatine *et al.*, 2004). The oxazepines and their fused derivatives (McGee *et al.*, 2005) have a wide range of biological activities, and form the basic skeleton of the alkaloids holstiine (**2**) (Cherif *et al.*, 1990) and concavine (**1**) (Fig. 1). Concavine, a novel alkaloid which was isolated from cultures of *Clitocybe concava* (Basidiomycota) in 2005, exhibits weak antibacterial activity (Arnone *et al.*, 2005). Structural modification of concavine and holstiine is required to confer stronger antibacterial activities to the compounds. Therefore, the synthesis of compounds containing the oxazepine (Levai, 2008; Yar *et al.*, 2009) or oxazocine (Neogi *et al.*, 2006) skeleton, respectively, has attracted considerable interest.

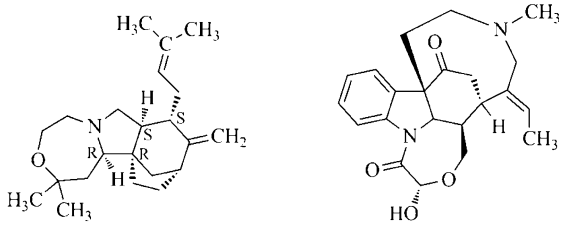
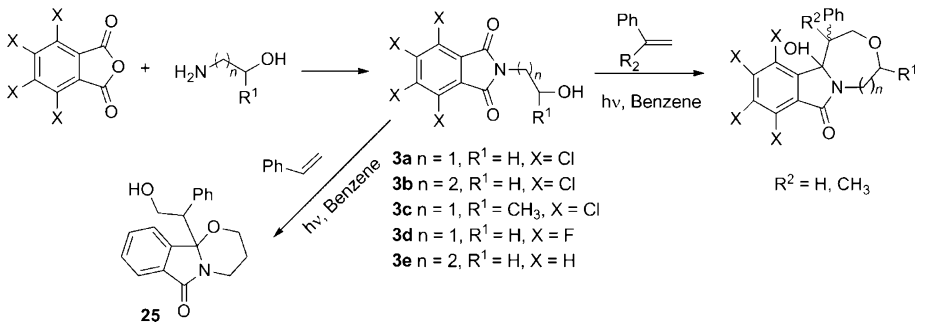


Fig. 1. Chemical structures of concavine (**1**) and holstiine (**2**).

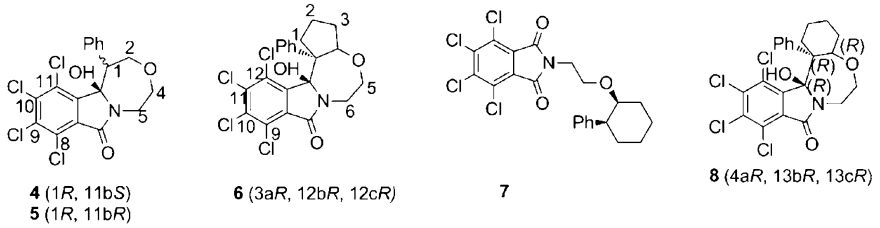
Recently, we have synthesized a series of annulated 7-membered oxazepine and 8-membered oxazocine derivatives, respectively, by employing a new strategy of intermolecular tandem reactions between *N*-(ω-hydroxyalkyl)-4,5,6,7-tetrachlorophthalimides and a series of acyclic and cyclic alkenes (Shen *et al.*, 2010; Xue *et al.*, 2000). Here we discuss the relationship between their structure and their antibacterial activity.

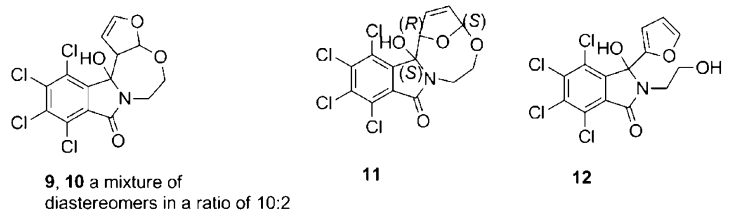
Results and Discussion

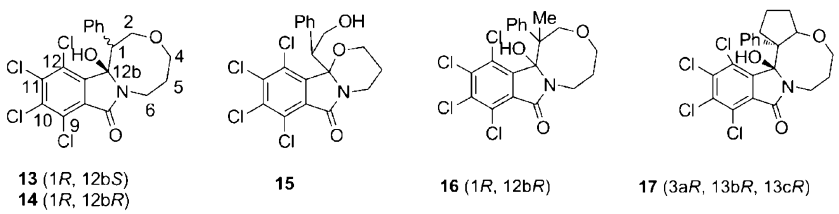
The starting materials **3a** – **3e** (Scheme 1) were obtained by reaction of tetrachlorophthalic anhydride and the corresponding amino alcohol. Subsequently, the final products were synthesized by photoinduced elec-

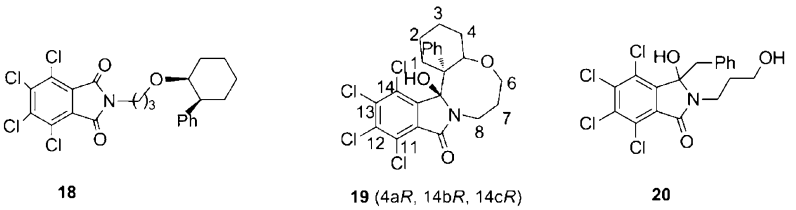


Scheme 1. General route for the preparation of compounds **3** and their corresponding cyclic derivatives.









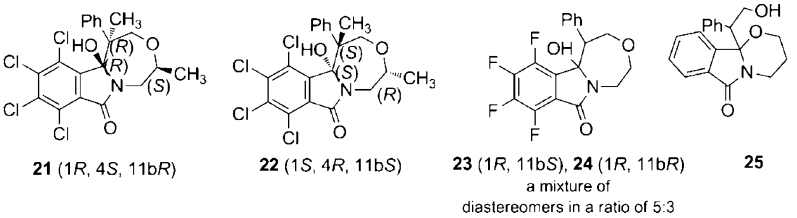


Fig. 2. Products and intermediates formed in photoreactions of a tetrachlorophthalimide **3** with an alkene.

tron transfer reactions between compounds **3a** – **3e** and several acyclic and cyclic alkenes. The structures of the synthesized compounds **4** – **20** (Fig. 2) were determined in our previous work (Shen *et al.*, 2010). The melting points were consistent with the literature data. Two new compounds, **21** and **22**, were synthesized using the same method, and their crystal structures were determined by X-ray diffraction (Figs. 3 and 4). Compounds **21** (1*R*, 4*S*, 11b*R*) and **22** (1*S*, 4*R*, 11b*S*) are a pair of diastereomers. Three stereogenic centres are created during the photocyclization, but only these two compounds were selectively synthesized. Photoreaction of **3d** with styrene gave the cyclization products **23** and **24** which were obtained as a mixture of diastereomers in a ratio of $\sim$ 5:3. Photoreaction of **3e** with styrene only gave the product **25**, which is a secondary product of the normal corresponding cyclization product. The crystal structure of **25** is shown in

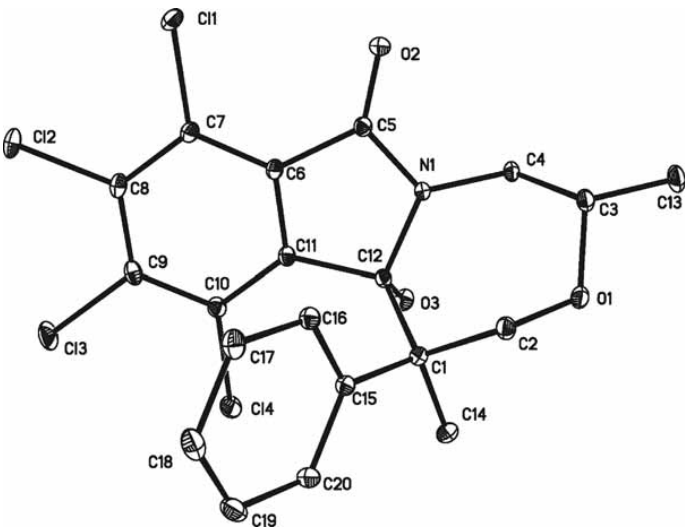


Fig. 3. An ORTEP view of compound **21**. Displacement ellipsoids are drawn at the 30 % probability level (the crystal cell was measured at room temperature).

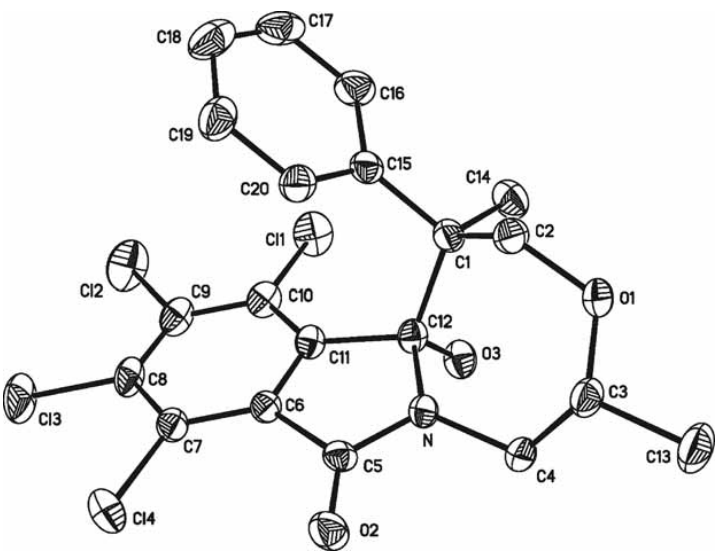


Fig. 4. An ORTEP view of compound **22**. Displacement ellipsoids are drawn at the 30 % probability level (the crystal cell was measured at room temperature).

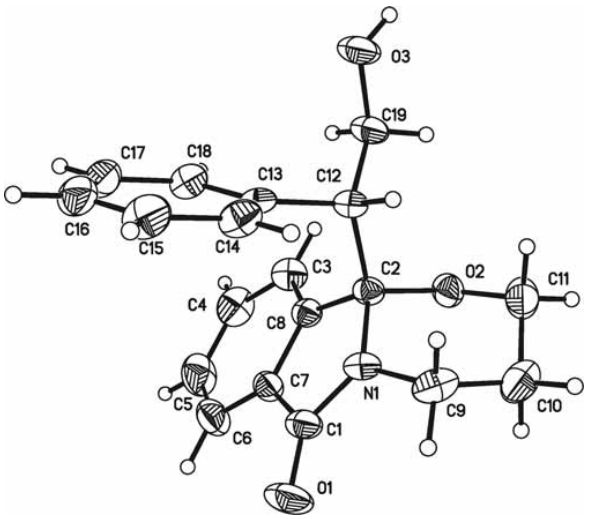


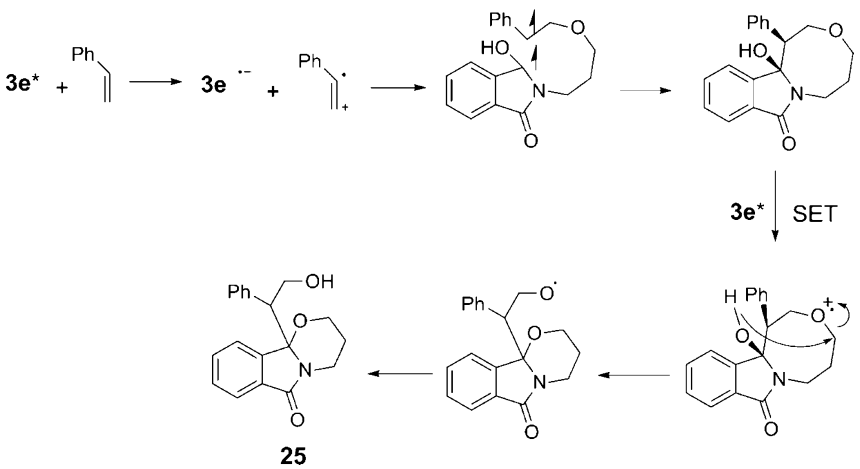
Fig. 5. An ORTEP view of compound **25**. Displacement ellipsoids are drawn at the 30% probability level (the crystal cell was measured at room temperature).

Fig. 5. A possible explanation for the formation of **25** is given in Scheme 2.

We evaluated compounds **3b** and **4**–**25** for their antimicrobial activities against two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas fluorescens*) bacteria, respectively. The starting material, compound **3b**, exhibited only a weak activity against *E. coli*. After the photocylization reaction, the antibacterial activities of the synthesized compounds were increased. As evident from Table I, the *cis*-compound **4** (1*R*, 11b*S*) exhibited a better activity against *S. aureus* than the *trans*-compound **5** (1*R*, 11b*R*) (*cis* and *trans* refer to the steric relationship between the hydroxy and the phenyl group, respectively; **4** and **5** are a diastereomeric pair) with respective MIC values of 12.5 μg/mL and 25 μg/mL, but **5** showed better antibacterial activity against *P. fluorescens* with a MIC value of 12.5 μg/mL. Likewise, the *cis*-compound **13** demonstrated moderate antibacterial activity against both *S. aureus* and *E. coli*, whereas the *trans*-compound **14** exhibited better antibacterial activity against *B. subtilis*. Of the diastereomers **21** and **22**, the first exhibited better antibacterial activity against the Gram-negative bacteria, the second against the Gram-positive bacteria. Thus, the steric structure of each compound had a considerable influence on its respective antimicrobial activity.

Compounds **9** and **10** were obtained as a mixture of diastereomers in a ratio of 10:2; they could not be separated from each other. The mixture of the diastereomers **9** and **10** exhibited better antibacterial activity against *B. subtilis* (MIC 6.25 μg/mL) than compound **11**. We found that compound **12** was formed in a secondary photoreaction of **11** under the reaction conditions (Shen *et al.*, 2010). Notably, compound **12** exhibited a broad antimicrobial spectrum against all four tested bacteria.

As can be seen from Table I, compound **18** exhibited the most potent antibacterial activity against *S. aureus* with a MIC value of 1.562 μg/mL, which is the same as that of the reference compound penicillin G, while the antibacterial activity of this compound against *E. coli* was as good as that of the reference compound kanamycin B (MIC 3.125 μg/mL). Thus, compound



Scheme 2. Proposed mechanism for the formation of compound **25**.

Table I. Antimicrobial activities of the synthesized compounds (MIC in $\mu g/mL$).

Compound	Microorganism			
	Gram-positive		Gram-negative	
	B. subtilis	*S. aureus*	*P. fluorescens*	*E. coli*
3b	> 50	> 50	> 50	25
4	25	12.5	> 50	25
5	> 50	25	12.5	> 50
6	12.5	25	> 50	25
7	12.5	12.5	12.5	> 50
8	25	> 50	> 50	25
9, **10**	6.25	> 50	12.5	25
11	25	25	25	12.5
12	6.25	3.125	12.5	6.25
13	25	6.25	> 50	6.25
14	6.25	> 50	12.5	25
15	> 50	6.25	25	25
16	25	12.5	12.5	12.5
17	12.5	> 50	> 50	12.5
18	3.125	1.562	6.25	3.125
19	6.25	6.25	12.5	25
20	1.562	3.125	12.5	6.25
21	> 50	25	6.25	12.5
22	12.5	3.125	> 50	25
23, **24**	> 50	50	> 50	25
25	> 50	> 50	> 50	50
Kanamycin B	0.39	1.562	3.125	3.125
Penicillin G	1.562	1.562	6.25	6.25

18 can be considered a potent broad-spectrum antibiotic. Compound **20** exhibited the best antibacterial activity against *B. subtilis*. It is noteworthy that three acyclic compounds exhibited better antibacterial activity than their corresponding cyclic analogues (*e. g.* **12** *vs.* **9** and **10**, **11**, and **18** *vs.* **17**).

The open-chain compounds exhibiting the highest activities can also be prepared by classical methods, however, their synthesis by this route is quite difficult (Chen *et al.*, 2004). Thus, our synthetic approach provides a new way to prepare these acyclic compounds under mild reaction conditions.

The length of the carbon chain also influences the antimicrobial activities: An additional carbon atom in compound **18** as compared to **7** greatly increased the antibacterial activity.

In order to evaluate the effect of the chlorine atoms in these compounds, we prepared three new compounds, **23**, **24**, and **25**, in which the chlorine atoms were substituted either by fluorine atoms (in **23** and **24**), or hydrogen atoms (in **25**). The antimicrobial activities were all decreased compared to the corresponding chlorine-substituted compounds (**23**, **24** *vs.* **4**, **5**, and **15** *vs.* **25**).

Conclusion

A series of concavine analogues were synthesized by the photoinduced cyclization of *N*-(ω-hydroxyalkyl)-4,5,6,7-tetrachlorophthalimides with alkenes. Most of them were found to have moderate to strong antibacterial activity. The relationships between steric structure and activity were discussed. Compounds **18** and **20** exhibited the highest antibacterial activities. The stereochemistry of the compounds greatly influenced the antimicrobial activities in that the acyclic compounds showed better antibacterial activity than their corresponding cyclic compounds, which could be synthesized by one simple step from the cyclic compounds.

Experimental

Materials

All chemicals were of analytical grade and were used without further purification. Most compounds used in this work were previously synthesized (Shen *et al.*, 2010). The five new compounds, **21**–**25**, were synthesized by the same method. Experimental details and instrumentation are given in Shen *et al.* (2010). Electrospray ionization mass spectra were obtained on a Thermo LCQ Fleet spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). CCDC 985313 (**22**), CCDC 985314 (**21**), and CCDC 1003598 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

*General procedure for the preparation of **3a**–**3e***

A solution of the corresponding amino alcohols was added dropwise to a mixture of tetrachlorophthalic anhydride and acetic acid under reflux conditions. After reflux for 1 h, the solution was cooled and filtered, and the crude product was recrystallized from acetic acid to get the pure product. Further experimental details are given in Shen *et al.* (2010).

*Photolysis of **3c** with α-methylstyrene*

A solution of **3c** (1.03 g, 3 mmol) and α-methylstyrene (3.12 g, 30 mmol) in benzene (120 mL) was photolyzed for 43 h to reach a 82% conversion of **3c**. The solvent was removed, and the residue was sepa-

rated to give **3c** (189 mg), **21** (385 mg, 34%), and **22** (482 mg, 43%).

*Compound **21***: White solid from ethyl acetate/petroleum ether. – M.p. 219 – 220 °C. – IR (KBr): ν = 3404, 2936, 1692, 1406, 1281, 1089, 729, 703 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3H, J = 6.1 Hz), 2.01 (s, 3H), 3.48 – 3.57 (m, 2H), 3.95 – 4.16 (m, 4H), 6.98 (s, 5H). – MS: m/z (%) = 459 $[M]^+$ (0.11), 414 (0.45), 412 (0.38), 326 (14), 311 (14), 309 (11), 298 (5.5), 296 (5.2), 118 (100), 117 (68), 103 (17), 91 (12). – $C_{20}H_{17}Cl_4NO_3$: found C 51.98, H 3.75, N 2.99; calcd. C 52.09, H 3.72, N 3.04.

X-ray structure analysis: $C_{20}H_{17}Cl_4NO_3 \cdot H_2O$, M = 479.16. Monoclinic, space group $P2_1/n$, a = 7.2761(2) Å, b = 13.2581(4) Å, c = 21.2732(6) Å, β = 95.378(2)°, V = 2043.13(10) $Å^3$, Z = 4, $D_{calcd.}$ = 1.558 g/cm^3. $F(000)$ = 984.0; absorption coefficient, 0.608 mm^{-1}; scan range for data collection, $1.81° \leq \theta \leq 29.99°$; measured reflections, 23,491; independent reflections, 5884; reflections with $I > 2\sigma(I)$, 5097; R_{int} = 0.0342; 239 refinable parameters; $R[F^2 > 2\sigma(F^2)]$ = 0.0318; $wR_2(F^2)$ = 0.0926.

*Compound **22***: White solid from ethyl acetate/petroleum ether. – M.p. > 300 °C. – IR (KBr): ν = 3367, 2978, 2931, 1691, 1397, 1353, 768, 728 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 1.33 (d, 3H, J = 6.3 Hz), 3.51 (d, 2H, J = 6.9 Hz), 3.77 (s, 1H), 4.41 (dd, 2H, J = 16.5, 11.7 Hz), 4.57 (hex, 1H, J = 6.6 Hz), 7.19 (t, 2H, J = 4.6 Hz), 7.44 – 7.46 (m, 2H), 8.60 – 8.63 (m, 1H). – MS: m/z (%) = 407 (0.2), 375 (30), 360 (100), 334 (17), 235 (7), 201 (4), 44 (3). – $C_{20}H_{17}Cl_4NO_3$: found C 52.03, H 3.75, N 3.02; calcd. C 52.09, H 3.72, N 3.04.

X-ray structure analysis: $C_{20}H_{17}Cl_4NO_3 \cdot H_2O$, M = 479.16. Monoclinic, space group $P2_1/n$, a = 7.3530(15) Å, b = 13.501(3) Å, c = 21.321(4) Å, β = 95.43(3)°, V = 2107.1(7) $Å^3$, Z = 4, $D_{calcd.}$ = 1.510 g/cm^3. $F(000)$ = 984.0; absorption coefficient, 0.589 mm^{-1}; scan range for data collection, $1.79° \leq \theta \leq 25.28°$; measured reflections, 4140; independent reflections, 3822; reflections with $I > 2\sigma(I)$, 2578; R_{int} = 0.0000; 239 refinable parameters; $R[F^2 > 2\sigma(F^2)]$ = 0.0477; $wR_2(F^2)$ = 0.1251.

*Photolysis of **3d** with styrene*

A solution of **3d** (0.448 g, 1.7 mmol) and styrene (1.77 g, 17.0 mmol) in benzene (70 mL) was photolyzed for 30 h to reach a 89% conversion of **3d**. The solvent was removed, and the residue was separated to give **3d** (49 mg), **23**, and **24** (345 mg, 62%).

*Compound **23***: White solid from ethyl acetate/petroleum ether. – M.p. 168 °C. – IR (KBr): ν = 1698, 1570, 1412, 1116, 719, 644 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 3.07 (dd, 1H, J = 9.6, 2.8 Hz), 3.57 – 3.64 (m, 1H), 3.84 (dd, 1H, J = 13.0, 3.4 Hz), 3.97 – 4.06 (m, 3H), 4.33 (s, 1H), 4.35 – 4.39 (m, 1H), 7.24 (dd, 2H, J = 7.4, 1.8 Hz), 7.30 – 7.15 (m, 3H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.4, 58.2, 66.7, 70.0, 92.2, 127.8, 128.3, 128.4, 128.5, 129.6, 137.3, 161.2. – ESI-MS: m/z = 368.00 $[M + H]^+$; calcd. 368.09. – $C_{18}H_{13}F_4NO_3$: found C 58.81, H 3.65, N 3.79; calcd. C 58.86, H 3.57, N 3.81.

*Compound **24***: ^1H NMR (400 MHz, $CDCl_3$): δ = 3.50 (dt, 1H, J = 10.8, 3.6 Hz), 3.72 (t, 1H, J = 2.4 Hz), 4.07 – 4.13 (m, 2H), 4.20 (dt, 1H, J = 12.8, 4.4 Hz), 4.32 – 4.35 (m, 1H), 4.47 (dd, 1H, J = 12.8, 3.2 Hz), 4.61 (s, 1H), 7.12 – 7.15 (m, 5H).

*Photolysis of **3e** with styrene*

A solution of **3e** (0.365 g, 1.9 mmol) and styrene (1.874 g, 18.0 mmol) in benzene (70 mL) was photolyzed for 30 h to reach a 62% conversion of **3e**. The solvent was removed, and the residue was separated to give **3e** (139 mg) and **25** (140 mg, 41%).

*Compound **25***: White solid from ethyl acetate/petroleum ether. – M.p. 165 – 166 °C. – IR (KBr): ν = 1676, 1641, 1562, 1415, 1065, 718, 645 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.72 – 1.91 (m, 2H), 3.39 (td, 1H, J = 13.0, 4.0 Hz), 4.00 – 4.04 (m, 1H), 4.18 – 4.25 (m, 2H), 4.37 (dd, 1H, J = 13.8, 5.4 Hz), 4.44 (dd, 1H, J = 12.2, 3.0 Hz), 4.48 – 4.51 (m, 1H), 6.58 – 6.61 (m, 2H), 7.01 (t, 2H, J = 7.2 Hz), 7.08 (tt, 1H, J = 7.4, 1.2 Hz), 7.50 (td, 1H, J = 7.4, 1.2 Hz), 7.62 – 7.66 (m, 2H), 7.72 (d, 1H, J = 8.0 Hz). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 35.0, 47.8, 61.8, 62.8, 91.6, 122.7, 123.7, 127.7, 128.2, 129.8, 130.0, 131.6, 132.6, 134.9, 143.8, 165.9. – ESI-MS: m/z = 310.08 $[M + H]^+$; calcd. 310.14. – $C_{19}H_{19}NO_3$: found C 73.73, H 6.22, N 4.52; calcd. C 73.77, H 6.19, N 4.53.

X-ray structure analysis: $C_{19}H_{19}NO_3$, M = 309.35. Triclinic, space group $P\bar{1}$, a = 9.255(6) Å, b = 9.299(6) Å, c = 10.208(7) Å, α = 91.173(11)°, β = 109.081(12)°, γ = 102.498(11)°, V = 806.5(9) $Å^3$, Z = 2, $D_{calcd.}$ = 1.274 g/cm^3. $F(000)$ = 328.0; absorption coefficient, 0.086 mm^{-1}; scan range for data collec-

tion, $2.12^\circ \leq \theta \leq 26.00^\circ$; measured reflections, 6977; independent reflections, 3161; reflections with $I > 2\sigma(I)$, 2063; $R_{\text{int}} = 0.0289$; 211 refinable parameters; $R[F^2 > 2\sigma(F^2)] = 0.0434$; $wR_2(F^2) = 0.1179$.

Biological assays

The antibacterial activity of the synthesized compounds was tested against two Gram-positive bacterial strains, *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 6538), and two Gram-negative bacterial strains, *Pseudomonas fluorescens* (ATCC 13525) and *Escherichia coli* (ATCC 35218), using MH (Mueller-Hinton) medium, containing 17.5 g casein hydrolysate, 1.5 g soluble starch, and 1000 mL beef extract. The MIC values of the test compounds were determined by a colorimetric method using the dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) (Meletiadis *et al.*, 2000). Stock solutions of the synthesized compounds (5 mg/mL) in dimethylsulfoxide (DMSO) were prepared, and graded quantities of the test compounds were incorporated in a specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtiter plates. A suspension of each microorganism was prepared to contain approximately 10^5 cfu/mL, applied to the microtiter plates to be tested, and incubated at 37 °C for 24 h. After the MIC values had been visually determined on each of the microtiter plates, 50 mL of PBS (phosphate-buffered saline) [0.01 mol/L, pH 7.4, $Na_2HPO_4 \cdot 12H_2O$ (2.9 g), KH_2PO_4 (0.2 g), NaCl (8.0 g), KCl (0.2 g), distilled water (1000 mL)] containing 2 mg of MTT/mL were added to each well. Incubation was continued at room temperature for 4 – 5 h. The content of each well was removed, and 100 μL of isopropanol containing 5 μL HCl (1 mol/L) were added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 570 nm. The observed MIC values are presented in Table I.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (NSFC 21202101) and Key Laboratory for Advanced Technology in Environmental Protection of Jiangsu Province (AE201306).

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