European Journal of Medicinal Chemistry 127 (2017) 166–173

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Syntheses and antibacterial activity of soluble 9-bromo substituted indolizinoquinoline-5,12-dione derivatives

Hui Yang [a, 1], Hao-Wen Wang [a, 1], Teng-Wei Zhu [a, 1], Le-Mao Yu [a], Jian-Wen Chen [a], Lu-Xia Wang [b], Lei Shi [b], Ding Li [a], Lian-Quan Gu [a], Zhi-Shu Huang [a], Lin-Kun An [a, *]

[a] School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, 510006, China
[b] Department of Clinical Laboratory, Guangzhou Liuhuaqiao Hospital, Guangzhou 510010, China

ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form
24 December 2016
Accepted 26 December 2016
Available online 27 December 2016

Keywords:
Indolizinoquinolinedione
Quinone
Antibacterial
Methicillin-resistant *Staphylococcus aureus*
Multi-drug resistance

ABSTRACT

In our previous research, 9-bromo indolizinoquinoline-5,12-dione **1** has been found to be a good anti-MRSA agent. However, it had very low bioavailability *in vivo* possibly due to its low solubility in water. In order to obtain the derivatives with higher anti-MRSA activity and good water solubility, twenty eight bromo-substituted indolizinoquinoline-5,12-dione derivatives were synthesized in the present study. The antibacterial activity of the synthesized compounds was evaluated against one gram-negative and some gram-positive bacterial strains including 100 clinical MRSA strains. The UV assays were carried out to determine the solubility of six active compounds **16, 21, 23** and **27**–**29**. The most potent compound **28** exhibited strong activity against clinical MRSA strains with both MIC_{50} and MIC_{90} values lower than 7.8 ng/mL. Compound **27** had good water solubility of 1.98 mg/mL and strong activity against clinical MRSA strains with MIC_{50} value of 63 ng/mL and MIC_{90} value of 125 ng/mL, 16-fold higher than that of Vancomycin.

1. Introduction

Over the past decades, the worldwide use of antibiotics has greatly improved public health. However, with the overuse and abuse of antibiotics, their efficacy rapidly decreasing. More and more drug-resistant bacteria, leading to increasing mortality rates, have been found [1,2]. Especially, methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant bacteria first reported in 1961 [3], has recently become one of the most important pathogenic bacteria that can lead to a variety of fatal infections, such as skin infections, sepsis, pneumonia, meningitis, and so on [4]. MRSA infections are very difficult to treat because they are resistant to various antibiotics. The antibiotic Vancomycin was called as the "antibiotic of last resort" for the treatment of MRSA infections. Unfortunately, Vancomycin-resistant bacteria has been first reported in 2002 [5]. The situation has led to an urgent need for discovery of new antibacterial agents.

Naphthoquinone derivatives have attracted wide attention because of their extensive biological activity, such as antitumor [6–9], antibacterial [9–13], antifungal [12,13], antimalarial [14,15], antitubercular [10], anti-inflammatory activity [16], etc. In our previous effort for the discovery of new antibacterial agents, we have found that a type of 9-bromo substituted indolizinoquinoline-5,12-dione derivatives exhibited strong antibacterial activity for gram-positive bacteria including MRSA [17]. The active compound **1** (Fig. 1) has shown strong inhibitory effect on the DNA gyrase supercoiling activity and DNA topoisomerase IV relaxing activity, possessing stronger anti-MRSA activity than Vancomycin with a minimum inhibition concentration (MIC) value of 63 ng/mL. Although compound **1** has shown good anti-MRSA activity *in vitro*, it has very low bioavailability in mouse model possibly due to its low water solubility. Here, we report our efforts for modification of compound **1** in order to obtain its derivatives with higher anti-MRSA activity and good water solubility. The antibacterial activity of the synthesized compounds were evaluated against one gram-negative and some gram-positive bacterial strains including 100 clinical MRSA strains.

* Corresponding author.
E-mail address: lssalk@mail.sysu.edu.cn (L.-K. An).
[1] These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.ejmech.2016.12.054
0223-5234/

2. Results and discussion

2.1. Design

Our previous structure-activity relationship (SAR) studies have shown that [18]: 1) The bromine at 9 position is important for the antibacterial activity. In comparison, the 9-chloro substituted analog has shown relatively lower activity for MRSA with MIC of 1 μg/mL 2) Although the 7-fluoro substituted analog has shown strong activity with the same MIC value as that of compound **1**, it had high cytotoxicity, which indicated it may not be a good choice for further development for good antibacterial agent [19]. 3) Alkylamino carbonyl substitution at 6-position has led to obviously decreased antibacterial activity possibly because of their lower solubility in water and organic solvents. 4) The presence and position of nitrogen atom in A ring have been found to be important for the activity. The analogs with nitrogen atom at 4 position or without nitrogen atom have shown obviously decreased antibacterial activity. On the other hand, alkoxy carbonyl substitution at 6-position has played important role for strong antibacterial activity.

In our previous study, we have found that the ester analogs with a longer side chain and amino terminal group at 6-position had higher water solubility than the parent compound **1**. Based on our previous SAR, twenty six ester analogs (**3**–**18** and **21**–**30**) were designed and synthesized in the present study, in which the corresponding ethyl group of compound **1** at 6-position was replaced with hydroxyalkyl group, phosphate group or alkylaminoalkyl group. In order to evaluate the effect of nitrogen atom in A ring on the antibacterial activity, compounds **31** and **32** were also designed and synthesized.

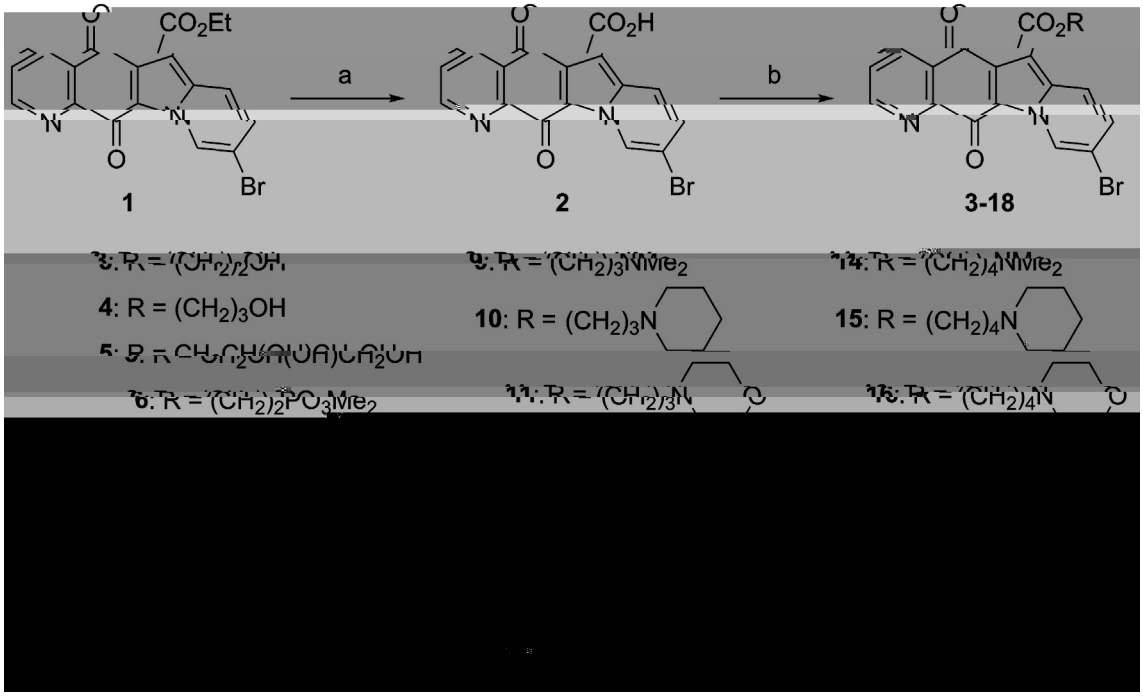
2.2. Chemistry

The syntheses of compounds **3**–**18** and **21**–**30** were depicted in Schemes 1 and 2. The acid **2** was obtained through hydrolysis of compound **1** with K_2CO_3 solution in isopropanol. Following acylchlorination of acid **2**, esterification gave the target esters **3**–**18** (Scheme 1). Due to the limitation of commercially available materials, the target esters **21**–**30** were synthesized through the reactions of the bromides **19** and **20** with the amines (Scheme 2). Compounds **21** and **26** were synthesized in a Pressure Vessel because the boiling point of reagent dimethylamine is low.

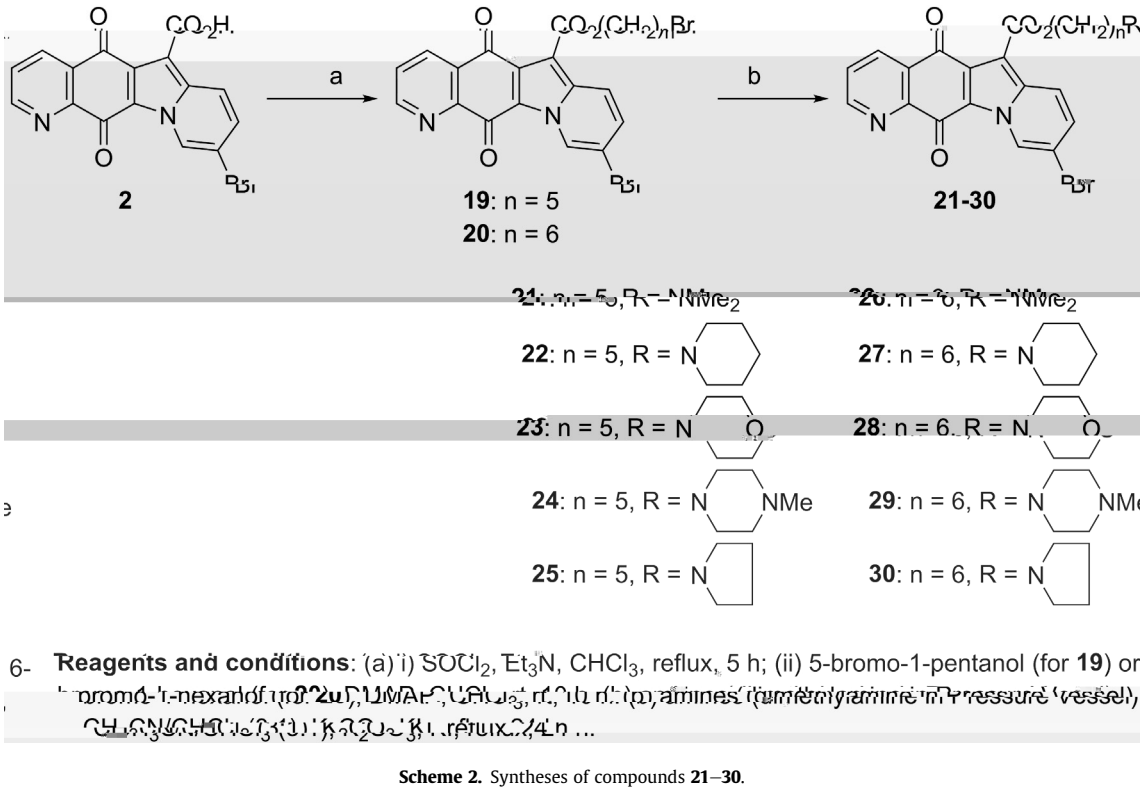
The compound **31** and **32** were synthesized as shown in Scheme 3. 6,7-Dichloroquinoxaline-5,8-dione, prepared in our lab as reported before [20], reacted with 3-bromopyridine and ethyl acetoacetate in ethanol solution to give two isomers **31** and **32**. The structures of these two isomers were elucidated by using HRMS and NMR spectra. In ^{1}H NMR spectrum of compound **31**, the singlet signal at 10.02 ppm indicated that bromine atom is at C-9 position. Based on the HRMS and NMR spectra, compound **31** was assigned as ethyl 8-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-*g*]quinoxaline-11-carboxylate. Similiarly, isomer **32** was assigned as ethyl 10-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-*g*]quinoxaline-11-carboxylate.

2.3. Antibacterial activity

The antibacterial activity of our synthesized compounds was first assessed by using a standard two-fold microdilution assay in Mueller-Hinton broth against one gram-negative bacterial strains (*E. coli*) and seven gram-positive bacterial strains, including *S. aureus* (ATCC 25922), *S. hemolytic-β* (CICC 10373), *S. pyogenes* (ATCC 19615), *S. pneumoniae* (ATCC 6305), *S. epidermidis* (ATCC 12228), *E. faecalis* (ATCC 29212) and MRSA (ATCC 25923) [21]. The minimum inhibition concentration (MIC) data were summarized as shown in Table 1. The results indicated that all synthesized compounds exhibited moderate to low antibacterial activity against *E. coli*. Six active compounds **16, 21, 23,** and **27**–**29** exhibited similar os1Tf1468.1h378.7Six20T13.802553339TCompoundsTF51Tf6.01890T.045



Scheme 1. Syntheses of compounds **3**–**18**.



Reagents and conditions: (a) i) $SOCl_2$, Et_3N, $CHCl_3$, reflux, 5 h; (ii) 5-bromo-1-pentanol (for **19**) or

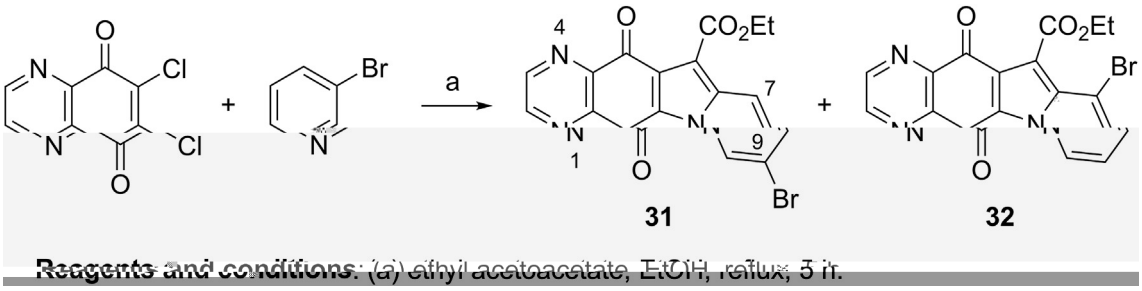
Scheme 2. Syntheses of compounds **21**–**30**.

MIC_{50} value of 63 ng/mL and MIC_{90} value of 125 ng/mL, 16-fold higher than that of Vancomycin, which implied that it could be further developed as an anti-MRSA lead compound.

4. Methods and materials

4.1. General experiments

The major chemical reagents for synthesis were purchased from Alfa Aesar, Sigma Aldrich Co or Aladdin Reagent Database Inc



Scheme 3. Syntheses of compounds **31**–**32**.

Table 1
The antibacterial activity of the synthesized compounds.

Cpd.	MIC (μg/mL)[a]							
	E. coli ATCC25922	*S. aureus* ATCC25923	MRSA ATCC43300	*S. hemolytic-β* CICC10373	*S. pyogenes* ATCC19615	*S. pneumoniae* ATCC6305	*S. epidermidis* ATCC12228	*E. faecalis* ATCC29212
1	>16	0.063	0.063	0.125	4	4	0.063	0.016
3	4	0.125	0.125	0.5	8	8	0.125	0.25
4	8	0.125	0.25	0.25	8	8	0.125	0.25
5	4	2	2	4	16	16	1	>16
6	16	1	1	1	16	16	0.5	0.5
7	1	2	2	8	8	16	1	8
8	0.5	0.5	0.5	0.5	8	4	0.031	0.5
9	1	1	1	2	16	8	0.25	2
10	8	4	4	2	16	16	0.5	4
11	16	0.5	0.5	4	16	16	0.25	2
12	>16	8	4	16	16	16	4	>16
13	0.5	2	1	2	8	4	0.25	1
14	1	4	2	4	16	8	0.25	2
15	4	1	1	2	16	4	0.125	1
16	>16	0.063	0.063	0.125	4	4	≤0.0078	0.25
17	8	0.25	0.5	1	8	2	0.031	0.5
18	1	2	1	4	8	4	0.125	1
21	1	≤0.0078	≤0.0078	0.25	2	0.5	≤0.0078	0.125
22	4	1	2	1	8	4	0.125	0.5
23	8	0.016	0.031	1	8	2	≤0.0078	0.25
24	2	0.25	0.25	0.25	8	2	≤0.0078	0.25
25	2	0.5	0.5	0.25	8	1	≤0.0078	0.5
26	2	0.25	0.25	0.5	8	2	≤0.0078	0.5
27	2	0.031	0.063	0.125	2	0.5	≤0.0078	0.125
28	8	≤0.0078	≤0.0078	0.031	2	0.5	≤0.0078	0.063
29	4	≤0.0078	≤0.0078	0.063	2	0.5	≤0.0078	0.25
30	1	0.5	0.5	2	4	1	≤0.0078	0.5
31	16	0.25	ND[b]	ND	ND	ND	ND	ND
32	>16	1	ND	ND	ND	ND	ND	ND
Pen	>16	0.063	>16	≤0.0078	≤0.0078	≤0.0078	8	1
Van[c]	ND	ND	2	ND	ND	ND	ND	ND

[a] The MIC values represent the results obtained in at least three independent experiments.
[b] "ND" means "not determined".
[c] "Van" means Vancomycin.

Table 2
The antibacterial activity of the active compounds for clinical MRSA strains.[a]

Cpd.	MIC (μg/mL)[b]								MIC_{50}[c] (μg/mL)	MIC_{90}[c] (μg/mL)
	202045	215073	122045	212014	305026	214026	219236	216054		
16	0.25	0.063	0.125	0.125	0.125	0.063	0.063	0.063	0.5	1
21	0.5	0.5	0.25	0.063	0.125	0.125	0.125	0.25	0.25	0.5
23	0.016	≤0.0078	0.063	0.063	0.063	0.063	0.031	0.063	0.031	0.125
27	≤0.0078	0.016	0.031	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	0.063	0.125
28	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078	≤0.0078
29	0.25	0.063	0.063	0.25	0.25	0.031	0.063	0.125	0.125	0.50
Van[d]	2	2	2	2	2	4	4	4	1	2

[a] These MRSA strains were clinically isolated in Guangzhou Liuhuaqiao Hospital, China.
[b] The MIC values represent the results obtained in at least three independent experiments. And more MIC values for clinical MRSA strains could be obtained from Supporting Information.
[c] MIC_{90} and MIC_{50} values were defined as the lowest concentration of compound at which 90% and 50% of MRSA were inhibited, respectively.
[d] "Van" means Vancomycin.

(Shanghai). The common solvents were obtained from local commercial suppliers and used without further purification unless otherwise indicated. Chemical reaction courses were monitored by using silica gel GF_{254} thin layer chromatography. The products were purified by using silica gel column chromatography (200–300 mesh). Melting points were determined in open capillary tubes on a MPA100 Optimelt Automated Melting Point System without being corrected. Nuclear magnetic resonance spectra were recorded on a Bruker AVANCE III 400 MHz spectrometer using tetramethylsilane as an internal reference. Mass spectra were analyzed on an Agilent 6120 (Quadrupole LC-MS) mass spectrometer. The high-resolution mass spectra were analyzed on a SHIMADZU LCMS-IT-TOF mass spectrometer. All compounds tested for biological activities were analyzed by using a SHIMADZU LC-20AT HPLC with SPD-20A detector and a Diamonsil C_{18} column (200 mm × 4.6 mm × 5.0 μm) and their purities were determined to be more than 95%.

*4.2. General procedure for the syntheses of compounds **3**–**20***

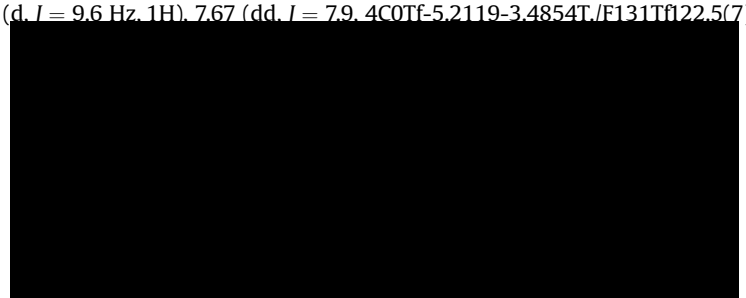
The syntheses of compounds **3**–**20** were carried out according to our previously reported method [17]. Briefly, at room temperature, the acid **2** (150 mg, 0.5 mmol) was acyl chlorinated with thionyl chloride (2.5 mL) and then esterized with various alcohol derivatives in chloroform. The reaction mixture was heated under reflux for 5 h to overnight, and cooled to room temperature. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography to give the target product.

*4.2.1. 2-Hydroxyethyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino [2,3-g]quinoline-6-carboxylate (**3**)*

Red solid, yield 46%, mp = 247.4–248.3 ^{O}C. ^{1}H NMR (DMSO) δ 9.84 (s, br, 1H), 9.01 (dd, J = 4.6, 1.6 Hz, 1H), 8.44 (dd, J = 7.9, 1.6 Hz, 1H), 8.22 (d, J = 9.6 Hz, 1H), 7.83 (dd, J = 7.9, 4.6 Hz, 1H), 7.78 (dd, J = 9.6, 1.7 Hz, 1H), 4.91 (t, J = 5.6 Hz, 1H), 4.37 (t, J = 5.2 Hz, 2H), 3.78 (q, J = 5.2 Hz, 2H). ^{13}C NMR (DMSO) δ 178.9, 173.1, 162.1, 154.4, 149.2, 137.4, 135.3, 132.1, 130.9, 128.0, 127.7, 127.4, 123.3, 121.9, 113.1, 106.1, 66.8, 59.4. HRMS (ESI) *m/z*: 436.9735 $[M+Na]^+$, calcd for $C_{18}H_{11}N_2O_5BrNa$ 436.9744.

*4.2.2. 3-Hydroxypropyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g]quinoline-6-carboxylate (**4**)*

Red solid, yield 42%, mp = 250.4–250.6 ^{O}C. ^{1}H NMR ($CDCl_3$) δ 10.10 (s, 1H), 9.05 (dd, J = 4.6, 1.5 Hz, 1H), 8.56 (dd, J = 7.9, 1.5 Hz, 1H), 8.34 (d, J = 9.6 Hz, 1H), 7.67 (dd, J = 7.9, 4C0Tf-5.2119-3.4854T./F131Tf122.5(7)-310.3((t,)]TJ/F31Tf9.07630TD(J)Tj/F131Tf()T1TD()Tj/F11T0.4(5TD



(m, 2H). ^{13}C NMR ($CDCl_3$) δ 178.8, 173.3, 162.7, 154.3, 149.2, 138.2, 135.5, 132.1, 130.9, 128.3, 127.7, 127.2, 122.8, 121.6, 113.6, 106.6, 63.7, 55.7, 54.4, 25.7, 25.3, 24.0. HRMS (ESI) *m/z*: 496.0869 $[M+H]^+$, calcd for $C_{24}H_{23}N_3O_4Br$ 496.0866.

*4.2.9. 3-Morpholinopropyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g]quinoline-6-carboxylate (**11**)*

Red solid, yield 67%, mp = 174.2–175.1 °C. ^{1}H NMR ($CDCl_3$) δ 10.11 (dd, *J* = 1.6, 0.8 Hz, 1H), 9.05 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.55 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.30–8.27 (m, 1H), 7.68 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.58–7.54 (m, 1H), 4.51 (t, *J* = 6.5 Hz, 2H), 3.76–3.72 (m, 4H), 2.64–2.59 (m, 2H), 2.52 (m, 4H), 2.11–2.02 (m, 2H). ^{13}C NMR (CDCl3) δ 178.7, 173.2, 162.8, 154.2, 149.1, 138.2, 135.5, 132.0, 130.9, 128.3, 127.6, 127.2, 122.7, 121.5, 113.5, 106.6, 66.9, 63.7, 55.4, 53.6, 25.7. HRMS (ESI) *m/z*: 498.0661 $[M+H]^+$, calcd for $C_{23}H_{21}N_3O_5Br$ 498.0659.

*4.2.10. 3-(4-Methylpiperazin-1-yl)propyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g]quinoline-6-carboxylate (**12**)*

Red solid, yield 76%, mp = 153.7–154.2 °C. ^{1}H NMR (CD_3OD) δ 9.49 (s, 1H), 8.82 (s, br, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 9.5 Hz, 1H), 7.74–7.67 (m, 1H), 7.48 (d, *J* = 9.5 Hz, 1H), 4.29 (t, *J* = 5.7 Hz, 2H), 3.18–2.83 (m, 10H), 2.71 (s, 3H), 2.09–2.00 (m, 2H). ^{13}C NMR (CD_3OD) δ 177.4, 172.2, 162.0, 153.5, 148.0, 137.8, 135.2, 132.1, 130.2, 127.7, 127.5, 126.5, 121.9, 120.8, 113.4, 105.4, 62.6, 53.7, 53.0, 50.3, 42.7, 24.9. HRMS (ESI) *m/z*: 511.0987 $[M+H]^+$, calcd for $C_{24}H_{24}N_4O_4Br$ 511.0975.

*4.2.11. 3-(Pyrrolidin-1-yl)propyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g]quinoline-6-carboxylate (**13**)*

Red solid, yield 71%, mp = 129.4–131.1 °C. ^{1}H NMR (CD_3OD) δ 9.48 (s, 1H), 8.78 (d, *J* = 3.7 Hz, 1H), 8.17 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.83 (d, *J* = 9.4 Hz, 1H), 7.66 (s, 1H), 7.44 (d, *J* = 9.5 Hz, 1H), 4.27 (t, *J* = 6.1 Hz, 2H), 3.04–2.91 (m, 6H), 2.13–2.04 (m, 2H), 2.02–1.94 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 178.7, 173.2, 162.7, 154.3, 149.1, 138.2, 135.4, 132.0, 130.9, 128.3, 127.7, 127.2, 122.8, 121.6, 113.5, 106.6, 63.5, 54.1, 53.0, 27.6, 23.5. HRMS (ESI) *m/z*: 482.0721 $[M+H]^+$, calcd for $C_{23}H_{21}N_3O_4Br$ 482.0710.

*4.2.12. 4-(Dimethylamino)butyl 9-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g]quinoline-6-carboxylate (**14**)*

Red solid, yield 67%, mp = 120.6–122.1 °C. ^{1}H NMR (CD_3OD) δ 9.76–9.71 (m, 1H), 8.92 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.22 (dd, *J* = 9.7 5 Hz, 1H), 8.86.4(.)

1H), 1.45 (t, J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 176.8, 171.9, 162.7, 148.2, 148.0, 145.7, 145.5, 138.7, 132.6, 128.4, 127.9, 122.3, 121.7, 114.1, 107.9, 61.6, 14.1. HRMS (ESI) *m/z*: 421.9743 $[M+Na]^+$, calcd for $C_{17}H_{10}N_3O_4BrNa$ 421.9747.

*4.4.2. Ethyl 10-bromo-5,12-dioxo-5,12-dihydroindolizino[2,3-g] quinoxaline-11-carboxylate (**32**)*

Red solid, yield 14%, mp = 248.0–249.5 °C. ^{1}H NMR ($CDCl_3$) δ 9.73 (d, J = 6.4 Hz, 1H), 8.96 (s, br, 1H), 8.93 (s, br, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.03 (t, J = 6.4 Hz, 1H), 4.52 (q, J = 7.2 Hz, 1H), 1.43 (t, J = 7.2 Hz, 1H). ^{13}C NMR (CD_3OD) δ 177.6, 171.0, 164.0, 148.3, 147.8, 146.7, 145.3, 134.1, 131.1, 127.4, 127.1, 121.1, 117.9, 114.2, 111.9, 62.8, 14.0. HRMS (ESI) *m/z*: 421.9731 $[M+Na]^+$, calcd for $C_{17}H_{10}N_3O_4BrNa$ 421.9747.

4.5. In vitro antimicrobial activity evaluation

The MIC values were determined by using the reported broth dilution method [21]. Briefly, the starting concentrations of tested compounds were 16 μg/mL. The solution of compound in DMSO (15 μL) was added to 285 μL of bacterial culture (5×10^5 cells/mL) at the first well of flat-bottomed 96-well tissue culture plates (JET BIOFIL®, JET BIO-CHEMICALS Intl., Inc, CANADA). The solution was then double-diluted. Bacterial culture solution containing appropriate compound (150 μL) was discarded at the last well in order to ensure 150 μL volume of bacterial culture in every well. The plate was incubated at 37 °C for 20–24 h in electro-heating standing-temperature cultivator before the measurement of absorbance value. The optical density values at 600 nm were measured using a multifunctional microplate reader (PowerWave™ XS2, BioTek® Instruments Inc, USA).

4.6. The UV assay for the solubility in water

The saturated solutions of compounds in water were prepared through shaking at 25 °C for 4 h, and then diluted to measure the absorbance at 260 nm. The solubility of compound in water was calculated based on the absorbance at 260 nm.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81373257) and Guangdong Science and Technology Projects (No. 2013A022100035, S2013010015609).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.12.054.

References

[1] A. Coates, Y. Hu, R. Bax, C. Page, The future challenges facing the development of new antimicrobial drugs, Nat. Rev. Drug Discov. 1 (2002) 895–910.
[2] D.I. Andersson, D. Hughes, Antibiotic resistance and its cost: is it possible to reverse resistance? Nat. Rev. Microbiol. 8 (2010) 260–271.
[3] M. Barber, Methicillin-resistant staphylococci, J. Clin. Path. 14 (1961) 385–393.
[4] Y. Ji, Methods in Molecular Biology. Methicillin-resistant Staphylococcus aureus (MRSA) Protocols, first ed., Humana Press Inc, Totowa, New Jersey, 2007.
[5] D.M. Sievert, M.L. Boulton, G. Stoltman, D. Johnson, M.G. Stobierski, F.P. Downes, P.A. Somsel, J.T. Rudrik, W. Brown, W. Hafeez, T. Lundstrom, E. Flanagan, R. Johnson, J. Mitchell, S. Chang, Staphyloccocus aureus resistant to vancomycin–United States 2002, Morb. Mortal. Wkly. Rep. 51 (2002) 565–567.
[6] S. Giorgi-Renault, J. Renault, P. Gebel-Servolles, M. Baron, C. Paoletti, S. Cros, M.-C. Bissery, F. Lavelle, G. Atassi, Heterocyclic quinones. 17. A new in vivo active antineoplastic drug: 6,7-Bis(1-aziridinyl)-4-[[3 -(N,N-dimethylamino) propyl]amino]-5,8-quinazolinedione, J. Med. Chem. 34 (1991) 38–46.
[7] H.-W. Yoo, M.-E. Suh, S.W. Park, Synthesis and Cytotoxicity of 2-Methyl-4,9-dihydro-1-substituted-1H-imidazo[4,5-g]quinoxaline-4,9-diones and 2,3-Disubstituted-5,10-pyrazino[2,3-g]quinoxalinediones, J. Med. Chem. 41 (1998) 4716–4722.
[8] J.M. Miguel del Corral, M.A. Castro, M. Gordaliza, M.L. Martin, A.M. Gamito, C. Cuevas, A.S. Feliciano, Synthesis and cytotoxicity of new heterocyclic terpenylnaphthoquinones, Bioorg. Med. Chem. 14 (2006) 2816–2827.
[9] T. Sreelatha, S. Kandhasamy, R. Dinesh, S. Shruthy, S. Shweta, D. Mukesh, D. Karunagaran, R. Balaji, N. Mathivanan, P.T. Perumal, Synthesis and SAR study of novel anticancer and antimicrobial naphthoquinone amide derivatives, Bioorg. Med. Chem. Lett. 24 (2014) 3647–3651.
[10] D. Dey, R. Ray, B. Hazra, Antitubercular and antibacterial activity of quinonoid natural products against multi-drug resistant clinical isolates, Phytother. Res. 28 (2014) 1014–1021.
[11] M. Janeczko, O.M. Demchuk, D. Strzelecka, K. Kubinski, M. Maslyk, NewDe-g]quHu82o(de