Design, Synthesis and *In Vitro* Antitubercular Evaluation of Isatin-ciprofloxacin Hybrids with Hydrogen Bonding Capacity

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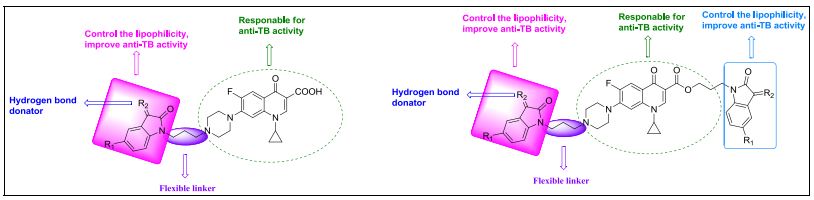


A series of novel isatin-ciprofloxacin hybrids inhaling oxime, semicarbazone, and thiosemicarbazone groups with hydrogen bonding capacity were designed, synthesized, and evaluated for their *in vitro* antitubercular activities against *Mycobacterium tuberculosis* (MTB) H37Rv and multidrug-resistant-TB (MDR-TB). All hybrids endowed with potential activities against the tested MTB H37Rv and MDR-TB strains with minimum inhibitory concentration (MIC) in a range of 0.20 to 128 μg/mL. In particular, the most active hybrid **5e** (MIC: 0.20 and 0.5 μg/mL) was four and two times more active than the parent ciprofloxacin (MIC: 0.78 μg/mL) and rifampicin (MIC: 0.39 μg/mL) against MTB H37Rv, and 4–>256 times more potent than the three references ciprofloxacin (MIC: 2.0 μg/mL), rifampicin (MIC: 32 μg/mL), and isoniazid (>128 μg/mL) against MDR-TB. Thus, this kind of hybrids holds great promise as future anti-TB agents against both drug-sensitive and drug-resistant MTB strains infection.

INTRODUCTION

Tuberculosis (TB), an old plague, caused mainly by infection *Mycobacterium tuberculosis* (MTB), remains one of the major global health problems [1,2]. According to the latest World Health Organization estimation, 10.4 million people fell ill with TB led to 1.7 million deaths in 2016 [3]. The first-line anti-TB drugs such as isoniazid (**INH**), rifampicin (**RIF**), pyrazinamide (**PZA**), and ethambutol (**EMB**) play a pivotal role in the treatment of TB patients, especially for the drug-susceptible TB patients, and 53 million lives were saved since the year 2000 mainly attributed to their contribution [3]. However, the new virulent forms of MTB such as drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), and extremely drug-resistant TB (XDR-TB) evolve and spread fast throughout the world, and have already increased up to alarming level in the recent decades. Moreover, only a handful of new anti-TB drugs have been introduced in the TB therapy after the discovery of **RIF** [4,5]. Several candidates are currently being under clinical evaluations for this purpose, but the number is far from sufficient [6]. Thus, it is imperative to develop novel anti-TB agent to prevent the spread of TB.

World Health Organization has recommended some of fluoroquinolones (FQs) exemplified by ciprofloxacin (Fig. 1) as second-line anti-TB agents for the treatment of primarily in cases involving resistance or intolerance to first-line anti-TB therapy [7,8]. Currently, MTB clinical isolates appear relatively low resistance to FQs, and the cross-resistance or antagonism of FQs with other classes of anti-TB agents was low [9–11]. Thus, rational design of FQs may provide more effective anti-TB candidates. The recent research results indicated that the lipophilicity of the FQs is vital for these compounds to overcome transport barrier into the MTB, and simply increment of lipophilicity may further improve their anti-TB potency [12,13]. Furthermore, the substituent at C-7 position influences greatly on the antibacterial potency, spectrum, and safety profiles of FQs, and the C-7 position of FQs motif is the most adaptable site for modification. Thus, incorporation of other pharmacophores with anti-TB potential into C-7 position of FQs may boost up their activities.

Isatin motif is a versatile structure for chemical modification, and its derivatives demonstrated promising anti-TB activities, so hybridization of isatin with FQs is a rationale strategy to develop new anti-TB candidates [6]. Recently, various FQs-isatin hybrids with improved lipophilicity were designed, synthesized, and screened for their *in vitro* and *in vivo* anti-TB activities [14–19]. The SAR revealed that the linker between FQs and isatin as

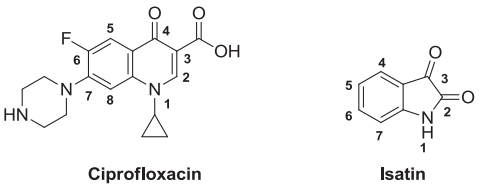


Figure 1. Chemical structures of ciprofloxacin and isatin.

well as substituents at C-3 and C-5 positions on isatin moiety have great influence on their anti-TB activities.

Based on the research results mentioned earlier and to continue our effort to develop new anti-TB agents, we designed, synthesized a series of propylene-tethered mono/bis-isatin-**CPFX** hybrids inhaling oxime, semicarbazone, and thiosemicarbazone groups with hydrogen bonding capacity, and evaluated for their *in vitro* antitubercular activities against MTB H37Rv and MDR-TB in this study. The design strategy was illustrated in Figure 2.

RESULTS AND DISCUSSION

The detailed synthetic route for propylene-tethered mono/bis-isatin-**CPFX** hybrids **5a–l** is depicted in Scheme 1. Alkylation of isatins **1a,b** with 1,3-dibromopropane in presence of K_2CO_3 to afford the intermediates *N*-(3-bromopropyl)isatins **2a,b**, which were then incorporated into **CPFX** motif to give mono-isatin-CPFX conjugates **3a,b** and bis-isatin-CPFX hybrids **4a,b**. Introduction of imines *via* condensations of requisite substituted amine hydrochlorides with hybrids **3a,b** and **4a, b** in presence of K_2CO_3 provided the desired products **5a–h**.

All hybrids **5a–l** were subsequently examined for their *in vitro* antitubercular activities against MTB H37Rv and MDR-TB (resistant to **INH**, **RIF**, and **EMB**), and the minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth and MICs are reported in Table 1.

It can be seen from Table 1 that all hybrids **5a–h** (Log *P*: 1.49–4.59) were much more lipophilic than the parent **CPFX** (Log *P*: 1.32), and the improved lipophilic character may be rendering them more capable to penetrate mycobacterial cell membrane, and consequently increase the anti-TB activity [15].

All hybrids exhibited considerable activities with MIC ranging from 0.2 to 128 μg/mL against MTB H37Rv and MDR-TB, and some of them were more potent than the parent **CPFX** (MIC: 0.78 and 1.0 μg/mL) against the tested two strains. The SAR revealed that mono-isatin-CPFX hybrids were more active than the corresponding bis-isatin-CPFX analogs, which may attribute that carboxylic acid at C-3 position is essential for gyrase binding and bacterial membrane transport [20], and also demonstrated that the lipophilicity was not the sole factor affected the anti-TB activity; for mono-isatin-CPFX series, hybrids with -Me at C-5 position on isatin skeleton were less potent than the corresponding unsubstituted derivatives, suggesting electron-donating group disfavored the activity; hydrogen bond donators at C-3 position on isatin moiety influenced the activity greatly, and the relative contribution order was thiosemicarbazone > semicarbazone > oxime, which may be due to the noncovalent interactions such as hydrophobic, electrostatic interactions, and metal chelation [16].

Among them, the most active hybrid **5e** with MIC of 0.20 and 0.5 μg/mL against the tested two strains was four and two times more active than the parent **CPFX** (MIC: 0.78 μg/mL) and **RIF** (MIC: 0.39 μg/mL) against MTB H37Rv, and 4–>256 times more potent than the three references **CPFX** (MIC: 2.0 μg/mL), **RIF** (MIC: 32 μg/mL), and **INH** (>128 μg/mL) against MDR-TB, demonstrating its potential to treatment of drug-sensitive and drug-resistant MTB infections. Moreover, the enriched SAR is conducive to further rational design of this kind of hybrids.

EXPERIMENTAL SECTION

Synthesis. ***General procedure for the preparation of intermediates 3a,b and 4a,b.*** *N*-(3-bromopropyl)isatins **2a,b** were obtained according to the literature reported method [19,20]. A mixture of *N*-(3-bromopropyl)isatins

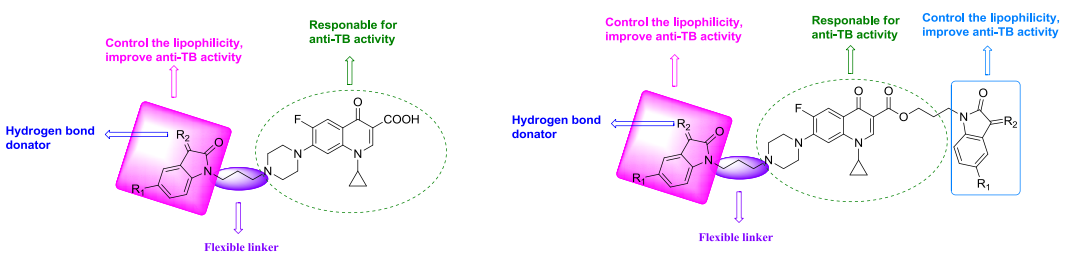
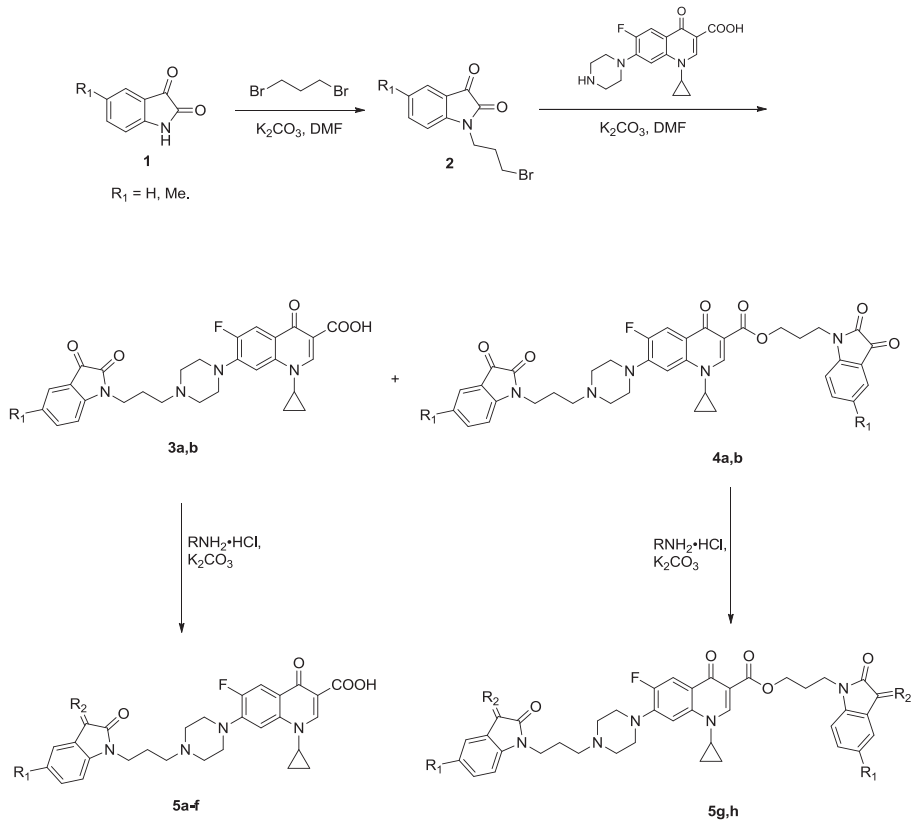


Figure 2. Illustration of the design strategy. TB, tuberculosis. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthetic route for hybrids **5a–h.**



2a,b (5 mmol), **CPFX** (3 mmol), and K_2CO_3 (20 mmol) was stirred at room temperature for 3 days. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase column with formic acid as additive to provide the desired the key intermediates **3a,b** and **4a,b**.

The general procedure for preparing targets 5a–h. To a solution of substituted amine hydrochlorides (15 mmol) and K_2CO_3 (15 mmol) dissolved in water (10 mL) and methanol (50 mL) was added **3a,b** or **4a,b** (5 mmol). The reaction mixture was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with water (20 mL), and then filtered. The solid crude product was purified by column chromatography (silica gel) eluted with DCM to *v*(DCM):*v*(MeOH) = 1:1 to give the title targets **5a–h**.

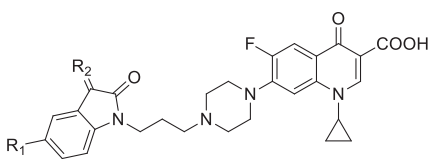
1-Cyclopropyl-6-fluoro-7-(4-(3-(3-(hydroxyimino)-2-oxoindolin-1-yl)propyl) piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (5a). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13–1.29 (4H, m, 2 × cyclopropyl-CH_2), 1.82 (2H, t, ─CH_2─), 2.40 (2H, t, ─CH_2─), 3.27–3.30 (4H, m, piperazine-4H), 3.58–3.61 (4H, m, piperazine-4H), 3.70 (2H, t, ─CH_2─), 4.11–4.12 (1H, m, cyclopropyl-CH), 7.06–7.72 (5H, m, Ar─H), 8.66 (1H, s, C2─H), 13.40 (1H, brs, NOH). ESI-MS m/z: 534 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{28}H_{28}FN_5O_5$: C, 63.03; H, 5.29; N, 13.13; Found: C, 62.87; H, 5.19; N, 13.01.

1-Cyclopropyl-6-fluoro-7-(4-(3-(3-(hydroxyimino)-5-methyl-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5b). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14–1.30 (4H, m, 2 × cyclopropyl-CH_2), 1.83 (2H, t, ─CH_2─), 2.25 (3H, s, CH_3), 2.43 (2H, t, ─CH_2─), 3.26–3.30 (4H, m, piperazine-4H), 3.55–3.58 (4H, m, piperazine-4H), 3.74 (2H, t, ─CH_2─), 4.10–4.12 (1H, m, cyclopropyl-CH), 7.10–7.74 (4H, m, Ar─H), 8.68 (1H, s, C2─H), 13.48 (1H, brs, NOH). ESI-MS m/z: 548 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{30}FN_5O_5$: C, 63.61; H, 5.52; N, 12.79; Found: C, 66.47; H, 5.33; N, 12.53.

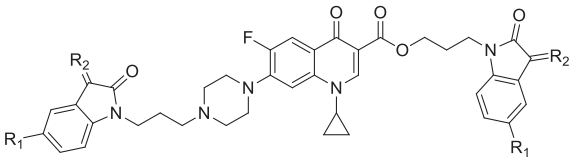
7-(4-(3-(3-(2-Carbamoylhydrazono)-2-oxoindolin-1-yl)propyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5c). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16–1.30 (4H, m, 2 × cyclopropyl-CH_2), 1.84 (2H, t, ─CH_2─), 2.42 (2H, t, ─CH_2─), 3.27–3.30 (4H, m, piperazine-4H), 3.60–3.63 (4H, m, piperazine-4H), 3.71 (2H, t, ─CH_2─), 4.11–4.13 (1H, m, cyclopropyl-CH), 7.09–7.76 (5H, m, Ar─H), 8.62 (1H, s, C2─H), 8.76, 8.84 (2H, brs, NNHCO$\underline{NH_2}$), 11.58 (1H, brs, N$\underline{NH}$CONH$_2$). ESI-MS m/z: 576 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{30}FN_7O_5$: C, 60.51; H, 5.25; N, 17.03; Found: C, 60.39; H, 5.06; N, 16.88.

Table 1

Structures, lipophilicity, and antitubercular activities of hybrids **5a–h.**



5a-f



5g,h

Compd.	R_1	R_2	Log *P* [a]	MIC (μg/mL)	
				MTB $H_{37}Rv$	[b]MDR-TB
5a	NOH	H	2.53	1.56	4.0
5b	NOH	Me	3.01	1.56	8.0
5c	$NNHCONH_2$	H	1.49	0.39	1.0
5d	$NNHCONH_2$	Me	1.98	0.78	1.0
5e	$NNHCSNH_2$	H	2.05	0.20	0.5
5f	$NNHCSNH_2$	Me	2.54	0.39	0.5
5g	NOH	H	3.61	100	64
5h	NOH	Me	4.59	50	128
CPFX			1.32	0.78	2.0
INH			−0.67	0.05	>128
RIF			3.71	0.39	32

MIC, minimum inhibitory concentration, MTB, Mycobacterium tuberculosis; INH, isoniazid; RIF, rifampicin.
[a]The Log *P* is calculated with ChemOffice 2012 software.
[b]MDR-TB: resistant to INH, RIF, and EMB.

7-(4-(3-(3-(2-Carbamoylhydrazono)-5-methyl-2-oxoindolin-1-yl)propyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5d). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18–1.30 (4H, m, 2 × cyclopropyl-CH_2), 1.81 (2H, t, ─CH_2─), 2.26 (3H, s, CH_3), 2.41 (2H, t, ─CH_2─), 3.28–3.30 (4H, m, piperazine-4H), 3.57–3.60 (4H, m, piperazine-4H), 3.72 (2H, t, ─CH_2─), 4.10–4.12 (1H, m, cyclopropyl-CH), 7.09–7.73 (4H, m, Ar─H), 8.63 (1H, s, C2─H), 8.79, 8.86 (2H, brs, NNHCO$\underline{NH_2}$), 11.56 (1H, brs, N$\underline{NH}$CONH_2). ESI-MS m/z: 590 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{32}FN_7O_5$: C, 61.11; H, 5.47; N, 16.63; Found: C, 61.03; H, 5.39; N, 16.37.

7-(4-(3-(3-(2-Carbamothioylhydrazono)-2-oxoindolin-1-yl) propyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5e). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19–1.28 (4H, m, 2 × cyclopropyl-CH_2), 1.81 (2H, t, ─CH_2─), 2.42 (2H, t, ─CH_2─), 3.27–3.30 (4H, m, piperazine-4H), 3.61–3.63 (4H, m, piperazine-4H), 3.72 (2H, t, ─CH_2─), 4.11–4.13 (1H, m, cyclopropyl-CH), 7.07–7.72 (5H, m, Ar─H), 8.64 (1H, s, C2─H), 8.78, 9.10 (2H, brs, NNHCS$\underline{NH_2}$), 12.08 (1H, s, N$\underline{NH}$CSNH_2). ESI-MS m/z: 592 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{30}FN_7O_4S$: C, 58.87; H, 5.11; N, 16.57; Found: C, 58.71; H, 4.95; N, 16.32.

7-(4-(3-(3-(2-Carbamothioylhydrazono)-5-methyl-2-oxoindolin-1-yl) propyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5f). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16–1.27 (4H, m, 2 × cyclopropyl-CH_2), 1.82 (2H, t, ─CH_2─), 2.25 (3H, s, CH_3), 2.42 (2H, t, ─CH_2─), 3.28–3.30 (4H, m, piperazine-4H), 3.58–3.60 (4H, m, piperazine-4H), 3.71 (2H, t, ─CH_2─), 4.11–4.13 (1H, m, cyclopropyl-CH), 7.09–7.71 (4H, m, Ar─H), 8.63 (1H, s, C2─H), 8.76, 9.08 (2H, brs, NNHCS$\underline{NH_2}$), 12.04 (1H, s, N$\underline{NH}$CSNH_2). ESI-MS m/z: 606 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{32}FN_7O_4S$: C, 59.49; H, 5.33; N, 16.19; Found: C, 59.24; H, 5.19; N, 16.07.

3-(3-(Hydroxyimino)-2-oxoindolin-1-yl)propyl 1-cyclopropyl-6-fluoro-7-(4-(3-(3-(hydroxyimino)-2-oxoindolin-1-yl)propyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (5g). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13–1.26 (4H, m, 2 × cyclopropyl-CH_2), 1.82 (2H, t, ─CH_2─), 2.03 (2H, t, ─CH_2─), 2.42 (2H, t, ─CH_2─), 3.25–3.28 (4H, m, piperazine-4H), 3.39–3.41 (4H, m, piperazine-4H), 3.75 (2H, t, ─CH_2─), 3.81–3.83 (1H, m, cyclopropyl-CH), 3.82 (2H, t, ─CH_2─), 4.21 (2H, t, ─CH_2─), 7.08–7.75 (10H, m, Ar─H), 8.42 (1H, s, C2─H), 13.44 (2H, brs, NOH). ESI-MS m/z: 736 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{39}H_{38}FN_7O_7$: C, 63.66; H, 5.21; N, 13.33; Found: C, 63.54; H, 5.11; N, 13.07.

3-(3-(Hydroxyimino)-5-methyl-2-oxoindolin-1-yl)propyl 1-cyclopropyl-6-fluoro-7-(4-(3-(3-(hydroxyimino)-5-methyl-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (5h). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15–1.30 (4H, m, 2 × cyclopropyl-CH_2), 1.84 (2H, t, ─CH_2─), 2.04 (2H, t, ─CH_2─), 2.45 (2H, t, ─CH_2─), 3.26–3.28 (4H, m, piperazine-4H), 3.40–3.43 (4H,

m, piperazine-4H), 3.73 (2H, t, ─CH_2─), 3.81 (2H, t, ─CH_2─), 3.88–3.90 (1H, m, cyclopropyl-CH), 4.22 (2H, t, ─CH_2─), 7.10–7.77 (10H, m, Ar─H), 8.46 (1H, s, C2─H), 13.46 (2H, brs, NOH). ESI-MS m/z: 764 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{41}H_{42}FN_7O_7$: C, 64.47; H, 5.54; N, 12.84; Found: C, 64.31; H, 5.34; N, 12.63.

MIC DETERMINATION

Hybrids **5a–h** together with **CPFX**, **RIF**, and **INH** were evaluated for their *in vitro* activities against MTB H37Rv and MDR-TB *via* rapid direct susceptibility test technique [19]. The wells of a sterile 48-well plate were filled with 100 mL two-fold diluted tested compounds and 100 mL MTB H37Rv or MDR-TB suspension containing 4×10^{-3} mg cells. Pure medium replaced the diluted compounds in two wells as the positive control of growth, and deionized water instead of the culture in other two wells as the negative control of growth in the plates. The plates were covered and sealed, then incubated at 37°C in a wet box. The positive and negative control wells should show obvious difference after 3 days. The MIC was determined by observing the quantity and state of the cells in each test well by a continuous visual high magnification system, and redetermined 7 days later. The MIC is defined as the concentration of the compound required to give complete inhibition of bacterial growth.

Conflict of Interests. The authors declare that there is no conflict of interests regarding the publication of this article.

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