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Synthesis and in vitro study of antibacterial, antifungal activities of some novel bisquinolines

Krishnendu B. Sahu · Soma Ghosh · Maitreyee Banerjee · Arindam Maity · Shyamal Mondal · Rupankar Paira · Pritam Saha · Subhendu Naskar · Abhijit Hazra · Sukdeb Banerjee · Amalesh Samanta · Nirup B. Mondal

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Abstract Efficient syntheses of a series of novel bisquinolines have been accomplished from 8-hydroxy quinolines under phase transfer catalyzed conditions using tetrabutylamoniumbromide as phase transfer catalyst. In vitro antibacterial and antifungal study of the synthesized analogues revealed six of them to show significant antibacterial and four to show significant antifungal activity. Among them **3c** and **6c** show most significant antibacterial activities with minimum inhibitory concentration value 32 μg/mL against four bacterial strains. Ultra structural studies of the microbes treated with **6c** demonstrated deformation of cell wall and cell agglomeration. The bisquinolines exhibiting bacteriostatic or fungistatic activity may be developed as newer antimicrobial agents.

Keywords Bisquinolines · Phase transfer catalysis · Bacteriostatic · Fungistatic

Introduction

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives prepared synthetically or isolated from natural resources are significant with respect to medicinal chemistry and biomedical use (Mistry and Jauhari, 2010). Many functionalized quinolines are often used for the design of many synthetic compounds with diverse pharmacological properties such as antibacterial (Dillard *et al.*, 1973; Chikhalia *et al.*, 2008), antifungal (Musiol *et al.*, 2006) and anti-protozoal activity (Hayat *et al.*, 2011), enzyme inhibitory (Dillard *et al.*, 1973), cytotoxic, (Kuo *et al.*, 1993), anti-inflammatory (Dillard *et al.*, 1973). Naturally occurring and various synthetic amino quinolines (Chloroquine, bis-quinolines) are potent antimalarial drugs. (Girault *et al.*, 2001; Gholap *et al.*, 2007) The quinolone drugs are potent inhibitors of lymphocyte apoptosis (Barchechath *et al.*, 2005). They often form the framework of DNA intercalating agents (Brana *et al.*, 2001; Martinez and Chacon-Garcia, 2005) and act as anticancer agents (Dominguez *et al.*, 2001). In addition, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals, and flavoring agents (Holla *et al.*, 2006). Moreover, 8-hydroxyquinoline and its metal complexes have been well known as antifungals for years (Musiol *et al.*, 2010). Structural similarities between quinoline based antifungals and terbinafine, (Gokhale and Kulkarni, 2000) is another interesting fact.

In this endeavor our approach is concerned with the synthesis of new chemical entities in search of newer antimicrobial agents based on quinoline (bisquinoline). The reported methods of bis-quinoline synthesis have some drawbacks, such as low yield, multistep reaction, and use of hazardous solvent (Raynes *et al.*, 1996). A previous report (Palit *et al.*, 2009) by our group describes the synthesis of a series of bisquinoline with limited resources, using quinoline and only some liquid dihaloalkanes (ethane, propane, butane, and pentane). In this endeavor our approach is concerned with the synthesis of new chemical

Electronic supplementary material The online version of this article (doi:10.1007/s00044-012-0011-4) contains supplementary material, which is available to authorized users.

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entities in search of newer antimicrobial agents based on quinoline. Herewith, we wish to report a one pot synthesis of a new class of quinoline dimers and their antibacterial as well as antifungal activities. We confined our approach to short preparation strategies using cheaper reagents, which may be amenable for future exploitation as multistep syntheses are seldom viable for commercialization. Phase transfer catalyzed reactions particularly appealed to us for the preparation of the desired product (Maruoka, 2008).

Results and discussion

Synthesis of quinoline dimer

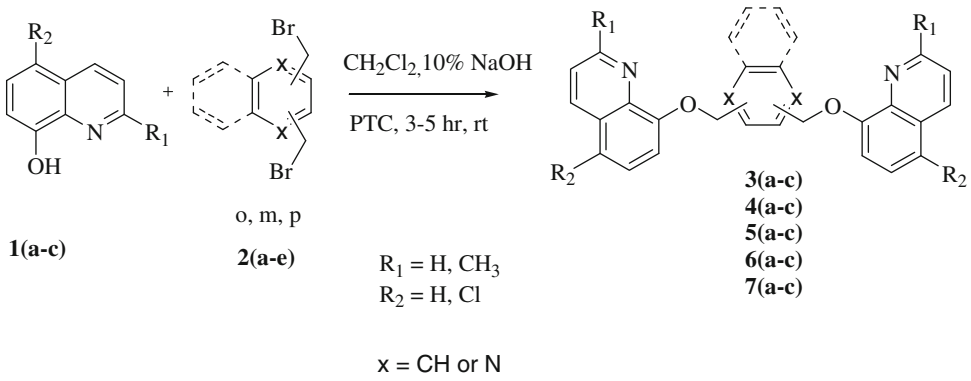
As a part of our quinoline based drug discovery program, we previously reported the synthesis and evaluation of a series of indolylquinoline, (Mahato *et al.*, 1994) anilidoquinoline (Ghosh *et al.*, 2008), and bis-quinoline (Palit *et al.*, 2009) derivatives which showed remarkable antiprotozoal, antiviral, and antibacterial activity. It is worthy of mention that in the formation of former bis-quinolines we utilized only a few dihaloalkanes as the alkylating agents. We contemplated to synthesize a different type of quinoline dimers by varying the miscellaneous alkylating agents like isomeric (*o*, *m*, *p*) dibromo xylenes, dibromo naphthalenes, and dibromo quinoxalines and reacting them with the differently substituted quinolines, viz. 8-hydroxy quinoline (**1a**), 2-methyl-8-hydroxy quinoline (**1b**), and 5-chloro-8-hydroxy quinoline (**1c**) and evaluate the products for their microbicidal properties.

Initially, the reaction of 8-hydroxyquinoline (**1a**) with α,α′-dibromo xylene (**2a**) in 2:1 molar ratio was studied under phase transfer catalytic condition and the progress of the reaction was monitored by thin layer chromatography (TLC). The reaction was observed to be completed within 3 h. Usual workup followed by chromatographic separation afforded the expected product, characterized as 1,2-bis-(8-quinolyloxymethyl)benzene (**3a**) from MS, ^{1}H, and ^{13}C NMR spectral analysis. This method was extended to differently substituted 8-hydroxyquinolines, viz. 2-methyl (**1b**) and 5-chloro (**1c**) derivatives. In all these cases bisquinolines (**3b–c**) were isolated in excellent yields. Isomeric bisquinolines were synthesized by the reaction of 8-hydroxyquinolines with *meta* (**2b**), and *para*-(**2c**) dibromo xylenes (Scheme 1; Table 1, entry **1–9**).

To explore the scope of this methodology with a more complex ring system, dibromo compound **2a** was replaced with 2,3-bis(bromomethyl)naphthalene **2d** (Scheme 1) and 2,3-bis (bromomethyl)benzo [*g*]quinoxaline **2e** (Scheme 1), which were allowed to react with 8-hydroxyquinolin (**1a**) and its substituted derivatives **1b** and **1c** (Scheme 1) under similar reaction conditions. The reactions appeared to be complete within 4 h and the corresponding bis-quinoline products were isolated in high yields (Table 1 entry **10–12** and **13–15**). It is also to be noted that very low yield of bisquinolines (26–42%) with long reaction time (24–48 h) and mixture of products (bisquinoline and quinolone) were obtained, when we used dihaloalkanes as electrofile (Palit *et al.*, 2009). But, using dibromo xylenes, dibromo naphthalene and dibromo quinoxaline no by product is formed with excellent yield of bisquinoline (82–95%) within 3–4 h. We presumed that the short reaction time is due to the greater reactivity of benzylic position of the electrophile.

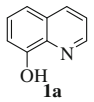
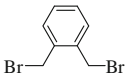
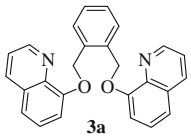
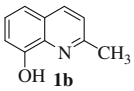
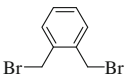
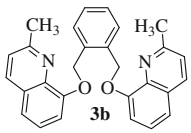
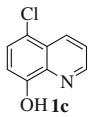
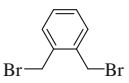
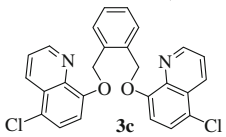
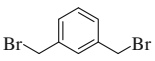
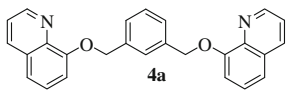
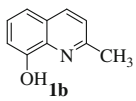
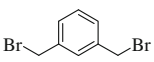
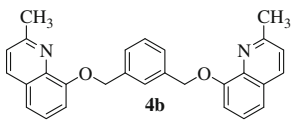
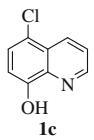
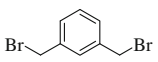
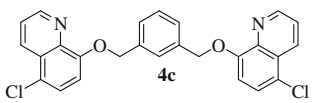
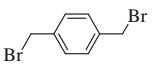
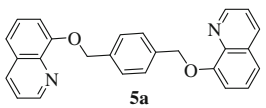
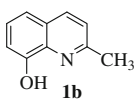
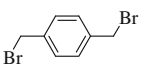
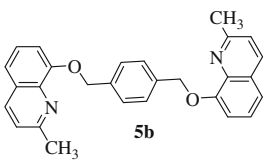
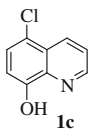
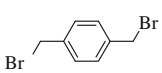
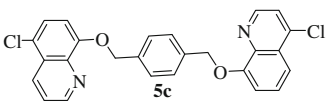
Antibacterial activity

All the synthesized compounds were tested for their antimicrobial and antifungal activities in vitro. The microorganisms used for antimicrobial study consisted of eight strains of bacteria, namely; *Staphylococcus aureus* 29737, *Micrococcus luteus* ATCC 9341, and *Bacillus pumilus* 11778 (all Gram-positive), as also *Shigella dysenteriae* 15, *Escherichia coli* 319, *Pseudomonas aeruginosa* 71, *Vibrio cholerae* 759, *Klebsiella pneumoniae* J/I/4 (all Gram-negative). Clinically used antibacterial agent gentamycin and amoxicillin were employed as the reference materials. Qualitative antimicrobial property of test samples was evaluated by disk diffusion method as per NCCLS protocol



Scheme 1 Reaction of 8-hydroxyquinolines with dibromoxylenes, dibromonaphthalenes, dibromoquinoxalenes using tetrabutylammonium bromide (TBAB) as phase transfer catalyst (PTC)

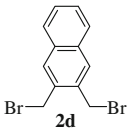
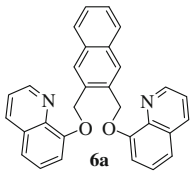
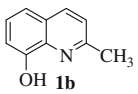
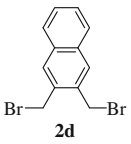
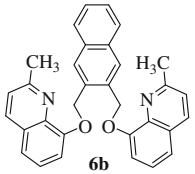
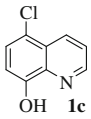
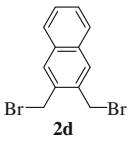
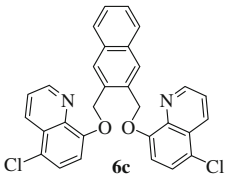
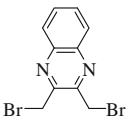
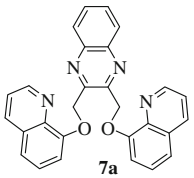
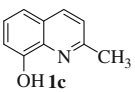
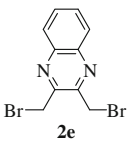
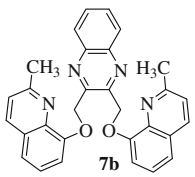
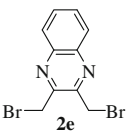
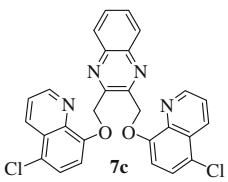
Table 1 Reaction of hydroxy quinolines with different alkylating agents

Entry no.	Hydroxy quinolines	Alkylating agent	Reaction time (hr)	Products[b]	Yield (%)[c]
1	 **1a**	 **2a**	3	 **3a**	88
2	 **1b**	 **2a**	5	 **3b**	85
3	 **1c**	 **2a**	4	 **3c**	80
4	 **1a**	 **2b**	4	 **4a**	90
5	 **1b**	 **2b**	4	 **4b**	95
6	 **1c**	 **2b**	3	 **4c**	88
7	 **1a**	 **2c**	3	 **5a**	90
8	 **1b**	 **2c**	3	 **5b**	83
9	 **1c**	 **2c**	4	 **5c**	82

(NCCLS protocol, 1993). The antimicrobial activities of the test samples were evaluated by determining the minimum inhibitory concentration (MIC) of the sample solution with respect to the standard drug. The results shown in Table 2 demonstrate that out of the tested compounds six (**3a**, **3b**, **3c**, **4c**, **6c**, **7c**) demonstrated a good degree of antimicrobial activity against bacteria.

The MIC tests revealed that **3c** had MIC between 32 and 128 μg/mL against seven organisms (*S. aureus* 29737, *S. dysenteriae* 15, *M. luteus* ATCC 9341, *E. coli* 319, *B. pumilus* 11778, *P. aeruginosa* 71, *V. cholerae* 759) and their zone diameters were found within 6–7 mm. Similarly, **3b** had MIC between 32 and 128 μg/mL against five strains viz. *S. dysenteriae* 15, *K. pneumoniae* J/I/4, *V. cholerae* 759, *S. aureus* 29737, *M. luteus* ATCC 9341 with their zone 6–8 mm. Likewise, compounds **6c** and **7c** had MIC between 32 and 128 μg/mL against five and three bacteria, respectively. The bacterial strains for **6c** were *M. luteus* ATCC 9341, *E. coli* 319, *B. pumilus* 11778, *K. pneumoniae* J/I/4, *V. cholerae* 759 and that for **7c** were *B. pumilus* 11778, *E. coli* 319, *M. luteus* ATCC 9341, and their zone diameters were also within 6–8 mm for each (Table 3). For the determination of the killing rate, the time dependent in vitro growth curves of *E. coli* 319 and *K. pneumoniae* J/I/4

Table 1 continued

Entry no.	Hydroxy quinolines	Alkylating agent	Reaction time[a] (hr)	Products[b]	Yield (%)[c]
10	 **1a**	 **2d**	3	 **6a**	88
11	 **1b**	 **2d**	3	 **6b**	85
12	 **1c**	 **2d**	4	 **6c**	92
13	 **1c**	 **2e**	4	 **7a**	80
14	 **1c**	 **2e**	4	 **7b**	80
15	 **1a**	 **2e**	3	 **7c**	88

All the reactions were carried out under PTC condition at room temperature

[a] All the products were characterized by 1H,13C NMR and mass spectroscopic techniques

[b] Isolated yield

at their MIC values were studied against test samples **3c** and **6c**, respectively (Figs. 1, 2).

A simple structure–activity relationship analysis of the compounds demonstrates that the orientation of the two quinoline rings attached to xylenes (*o*, *m*, *p*) plays a pivotal role in the microbial inhibition potentiality. For instance, compounds **3a–c** (two quinolyloxy groups ortho to each other) show much better antimicrobial activity than **4a–c** and **5a–c**, where the groups are *meta* and *para* to each other. Moreover, the presence of chlorine substitution in the quinoline ring enhanced the antimicrobial potentiality. However, the activity was significantly reduced in the presence of additional heteroaromatic rings **7a–c**.

The antimicrobial activity of test drugs revealed that Gram-negative bacteria were more susceptible to the test drug than Gram-positive ones. It is presumed that their thinner cell wall consisting of peptidoglycan network may allow rapid absorption of the drug into the cell. It is also related to the ability of the drugs to modify the DNA replication mechanism as well as to cause abnormalities in the size, and change in cytoplasmic contents, cell membrane, and outer cell layers of sensitive cells. (Hayatm, 1981).

To observe the change of bacterial cell on drug treatment, we studied the SEM micrographs (Fig. 3) after and before administration of drug to the bacterial cell. The observation clearly indicates that the bacteria changed its

Table 2 Antibacterial activity of test compounds against different bacterial strains

Name of the organisms	MIC (μg/ml) of test drugs and standard antibiotics																
	3a	**3b**	**3c**	**4a**	**4b**	**4c**	**5a**	**5b**	**5c**	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**	GT	AM
Staphylococcus aureus 29737	32	128	128	–	–	128	–	–	–	>500	>500	>500	–	–	>500	1	0.5
Shigella dysenteriae 15	32	32	64	–	–	32	–	–	–	>500	>500	>500	–	–	>500	2	100
Micrococcus luteus ATCC 9341	>500	128	32	–	–	64	–	–	–	>500	>1000	32	–	–	32	24	1
Escherichia coli 319	>500	>1000	32	–	–	>500	–	–	–	32	>500	32	–	–	32	0.5	4
Bacillus pumilus 11778	500	>500	32	–	–	>500	–	–	–	256	64	32	–	–	32	10	0.5
Pseudomonas aeruginosa 71	>500	>500	64	–	–	256	–	–	–	>500	>500	>500	–	–	>500	4	256
Vibrio cholerae 759	>500	64	32	–	–	256	–	–	–	>500	>500	128	–	–	>500	2	256
Klebsiella pneumoniae J/I/4	32	32	>500	–	–	32	–	–	–	>500	>1000	32	–	–	>500	0.25	256

GT gentamycin, *AM* amoxicillin

'–' No activity

Table 3 Zone of inhibition tests of the active compounds

Name of the organism	Diameter of zone of inhibition at MIC in mm									
	3a	**3b**	**3c**	**4c**	**6a**	**6b**	**6c**	**7c**	GT	AM
Staphylococcus Aureus 29737	7.2 ± 0.20	6.0 ± 0.20	7.0 ± 0.10	8.0 ± 0.15	6.0 ± 0.10	6.1 ± 0.20	6.0 ± 0.25	–	9.0 ± 0.87	10.5 ± 0.9
Shigella dysenteriae 15	6.5 ± 0.17	8.0 ± 0.10	6.0 ± 0.30	8.0 ± 0.20	6.0 ± 0.10	8.0 ± 0.05	–	6.0 ± 0.10	12.0 ± 0.5	9.5 ± 0.5
Micrococcus luteus ATCC 9341	7.0 ± 0.10	7.0 ± 0.70	6.5 ± 0.25	8.0 ± 0.25	6.0 ± 0.20	–	8.0 ± 0.00	7.0 ± 0.17	7.0 ± 0.5	11.0 ± 1.05
Escherichia coli 319	–	–	6.5 ± 0.20	–	9.7 ± 0.10	7.0 ± 0.05	7.2 ± 0.00	8.0 ± 0.20	9.0 ± 1.07	8.0 ± 0.87
Bacillus pumilus 11778	–	7.0 ± 0.20	6.0 ± 0.20	–	9.0 ± 0.25	6.0 ± 0.50	8.0 ± 0.02	8.0 ± 0.30	7.0 ± 0.68	10.0 ± 0.72
Pseudomonas aeruginosa 71	6.0 ± 0.20	–	7.5 ± 0.15	6.0 ± 0.15	8.2 ± 0.20	–	–	–	9.0 ± 0.86	7.5 ± 0.61
Vibrio cholerae 759	–	8.0 ± 0.10	7.0 ± 0.20	6.0 ± 0.20	7.1 ± 0.20	–	8.0 ± 0.15	–	11.0 ± 1.65	7.0 ± 0.5
Klebsiella pneumoniae J/I/4	8.0 ± 0.24	8.0 ± 0.20	–	6.0 ± 0.01	6.4 ± 0.10	–	7.0 ± 0.20	6.0 ± 0.25	9.0 ± 0.6	8.0 ± 0.93

– shows no measurable zone of inhibition

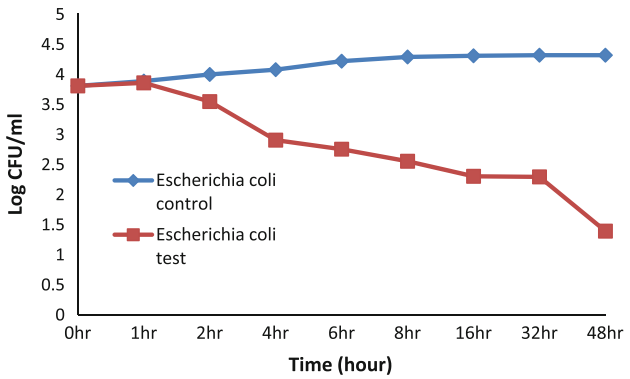


Fig. 1 Time dependent in vitro growth curve of *E. coli* 319 at the MIC values against test sample **3c**

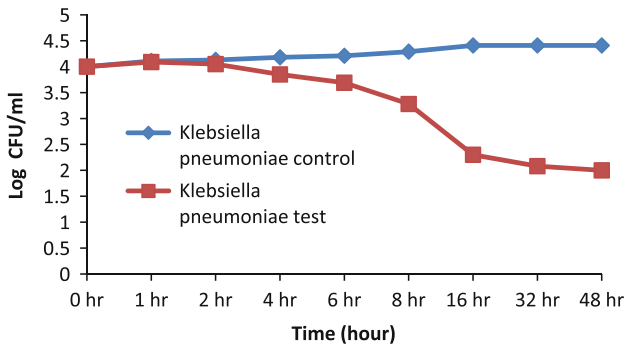


Fig. 2 Time dependent in vitro growth curve of *Klebsiella pneumoniae* J/I/4 at the MIC values against test sample **6c**

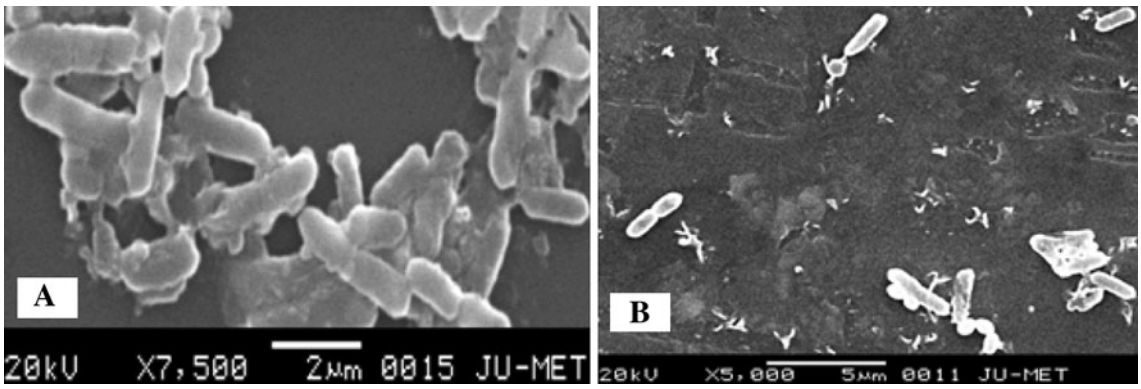


Fig. 3 The SEM micrographs of *Klebsiella pneumoniae* J/I/4: **a** after treatment; **b** before treatment with test drug **6c** against the MIC concentration

Table 4 Antifungal activities of chemically synthetic compound against different fungi strains

Name of the organism	MIC (μg/ml) of test drugs[a]															
	3a	**3b**	**3c**	**4a**	**4b**	**4c**	**5a**	**5b**	**5c**	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**	Fluconazole
Aspergillus niger	–	1,000	1,000	–	–	1,000	–	–	–	–	–	–	–	–	1,000	10
Candida albicans	–	–	1,500	–	–	–	–	–	–	–	–	–	–	–	1000	04
Candida tropicalis	–	2,000	1,000	–	–	1,000	–	–	–	–	–	–	–	–	1500	08
Cryptococcus neoformans	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	08

– no activity

[a] With respect to fluconazole; a standard antifungal antibiotic

Table 5 Zone of inhibition of the tested compounds

Name of the organism	Diameter of zone of inhibition at MIC in mm								
	3a	**3b**	**3c**	**4a**	**4b**	**4c**	**5a**	**7c**	Fluconazole
Aspergillus niger	–	9.0 ± 0.50	7.5 ± 0.02	–	–	8.0 ± 0.17		7.5 ± 0.20	8.6 ± 0.5
Candida albicans	–	–	7.0 ± 0.30	–	–	–	–	7.8 ± 0.30	10.2 ± 0.83
Candida tropicalis	–	7.0 ± 0.30	9.0 ± 0.13	–	–	7.0 ± 0.10		7.5 ± 0.20	8.5 ± 0.5
Cryptococcus neoformans	–	–	–	–	–	–	–	–	8.5 ± 0.96

'–' shows no measurable zone of inhibition

morphology after drug treatment. In case of *K. pneumoniae* J/I/4 the cell walls were deformed, became uneven and the cells were agglomerated. So we presume that the antimicrobial activity of synthesized drugs is due to damage of microbial enzyme or cell wall permeability.

Antifungal studies were carried out on four strains of fungi, viz. *Aspergillus niger*, *Candida albicans*, *Candida tropicalis*, *Cryptococcus neoformans.* Among all the drugs, only **3c**, **3b**, **4c**, and **7c** showed activity against three fungi, viz. *A. niger*, *C. albicans, and C. tropicalis*, which had MIC value 1000–2000 μg/mL (Table 4) and the zone diameter of inhibition in between 7 and 9 mm (Table 5). However, these drugs did not show any recognizable antifungal activity against *Cryptococcus neoformans.*

Conclusion

In summary, we have shown a general and effective method for the synthesis of bis-quinolines based on PTC mediated alkylation. This procedure allows a great deal of synthetic flexibility and offers the possibility of synthesizing newer heteroaromatic systems having potential biological activity. The salient features of this methodology are that it works with inexpensive and easily available reactants operating in an environment friendly, mild reaction condition with operational simplicity. Of the fifteen compounds six showed significant antibacterial actions and four showed considerable antifungal activity. The compounds exhibited bacteriostatic or fungistatic activity and may be developed as newer antimicrobial agents.

Experimental

Chemistry

Materials and methods

All the compounds (Table 1) evaluated in this work were synthesized in one-pot sequences. The 8-OH quinoline and naphthalene derivatives, 1,4-dibromobutane-2,3-dione, used for the preparation of quinoxaline (Paira *et al.*, 2009) NBS (used for the bromination of dimethyl naphthaline (Paira *et al.*, 2010) and PTC (TBAB) were purchased from Aldrich Chemical Company Ltd (USA). The organic solvents used for the chemical syntheses and chromatography were acquired from E. Merck (India) and were of analytical grade. Melting points were determined in capillaries and are uncorrected. The NMR spectra were recorded using a BRUKER DPX 300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C nuclei, using TMS as internal standard. Mass spectra (positive mode) were obtained on a Micro mass Q-TOF micro^{TM} spectrometer in the electrospray mode. Column chromatography was performed on silica gel 60 (E. Merck India, Mumbai). TLC was performed on Merck $60F_{254}$ pre-coated silica gel 60 plates. Compounds were visualized with UV light or on heating after spraying Liebermann–Burchard reagent as developing agent.

General method of preparation of compounds ***3a–c***, ***4a–c***, ***5a–c***, ***6a–c*** *and* ***7a–c*** Appropriate amount of 8-hydroxy quinolines (10 mmol) or its analogues was dissolved in excess of CH_2Cl_2 (50 ml) followed by the addition of required amount (2:1 molar ratio) of α,α'-dibromo xylenes. Aqueous solution of NaOH (10%, 50 ml) was added followed by a pinch of PTC (tetra butyl ammonium bromide). The mixture was stirred continuously at room temperature. A series of color changes was observed in the reaction vessel which became colorless after 2–3 h. The reaction was found to be complete (monitored by TLC) within 5 h. The organic layer was separated, washed twice with water, dried over anhydrous Na_2SO_4, and then evaporated to dryness. The crude product was separated by column chromatography and crystallized. All the reaction products were characterized from their ^{1}H and ^{13}C NMR, mass spectral and HRMS analyses.

1,2-Bis-(8-quinolyloxymethyl)benzene ***3a*** White solid, Mp 172–173 °C; R_f (1% MeOH–$CHCl_3$) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (4H, s), 7.11–7.14 (2H, m), 7.26–7.34 (6H, m), 7.39–7.42 (2H, m), 7.58–7.61 (2H, m), 8.07–8.10 (2H, m), 8.92–8.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.0 (2 × CH_2), 109.8 (2 × CH), 119.7 (2 × CH), 121.4 (2 × CH), 126.4 (2 × CH), 128.1 (2 × C), 128.6 (2 × CH), 129.2 (2 × C), 134.8 (2 × C), 135.7 (2 × CH), 140.2 (2 × C), 149.1 (2 × C), 154.0 (2 × C). HRMS [ESI], m/z calcd for $C_{26}H_{20}N_2O_2Na$: $[M+Na]^+$ 415.1422: found 415.1439.

1,2-Bis-(2-methyl-8-quinolyloxymethyl)benzene ***3b*** White solid, Mp 170–172 °C; R_f (1% MeOH–$CHCl_3$) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (6H, s), 5.65 (4H, s), 7.05–7.08 (2H, m), 7.18–7.30 (8H, m), 7.59–7.62 (2H, m), 7.91 (2H, d $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (2 × CH_3), 69.2 (2 × CH_2), 110.2 (2 × CH), 119.6 (2 × CH), 122.2 (2 × CH), 125.3 (2 × CH), 127.4 (2 × C), 127.7 (2 × CH), 128.1 (2 × CH), 134.9 (2 × C), 135.7 (2 × CH), 139.9 (2 × C), 153.5 (2 × C), 157.8 (2 × C). HRMS [ESI], m/z calcd for $C_{28}H_{24}N_2O_2Na$: $[M+Na]^+$ 443.1735: found 443.1745.

1,2-Bis-(5-chloro-8-quinolyloxymethyl)benzene ***3c*** White solid, Mp 190–193 °C; R_f (1% MeOH–$CHCl_3$) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (4H, s), 6.93 (2H, d $J = 8.4$ Hz) 7.20 (2H, d $J = 8.4$Hz) 7.31–7.35 (2H, m) 7.46–7.55 (4H, m) 8.43 (2H, dd $J = 8.7$, 1.5 Hz) 8.90 (2H, dd $J = 4.2$, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.9 (2 × CH_2), 109.7 (2 × CH), 122.1 (2 × CH), 125.9 (2 × CH), 126.7 (2 × C), 128.4 (2 × CH), 129.1 (2 × CH), 132.3 (2 × CH), 134.7, (4 × C) 140.6 (2 × C), 149.5 (2 × CH), 153.3 (2 × C). HRMS [ESI], m/z calcd for $C_{26}H_{18}Cl_2N_2O_2Na$: $[M+Na]^+$ 483.0643: found 483.0634.

1,3-Bis-(8-quinolyloxymethyl)benzene ***4a*** White solid, Mp 111–113 °C; R_f (1% MeOH–$CHCl_3$) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (4H, s), 6.97 (2H, dd $J = 2.1$, 6.6 Hz), 7.27–7.34 (5H, m), 7.36–7.40 (2H, m), 7.44–7.47 (2H, m), 7.65 (1H, s), 8.08 (2H, dd $J = 1.5$, 6.9 Hz), 8.93–8.95 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.5 (2 × CH_2), 109.8 (CH), 109.9 (CH), 119.8 (2 × CH), 121.5 (2 × CH), 125.7 (2 × C), 126.4 (2 × CH), 126.5 (2 × CH), 128.9 (2 × C), 129.4 (CH), 135.7 (CH), 135.8 (CH), 137.3 (CH), 140.4 (2 × C), 149.2 (2 × CH), 154.1 (C), 154.2 (C). HRMS [ESI], m/z calcd for $C_{26}H_{20}N_2O_2Na$: $[M+Na]^+$ 415.1422: found 415.1443.

1,3-Bis-(2-methyl-8-quinolyloxymethyl)benzene ***4b*** White solid, Mp 109–111 °C; R_f (1% MeOH–$CHCl_3$) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (6H, s), 5.45 (4H, s), 6.96 (2H, d $J = 7.2$ Hz), 7.29–7.30 (6H, m), 7.37 (1H, d $J = 7.8$ Hz), 7.46 (2H, m), 7.65 (1H, s), 7.99 (2H, d $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6 (2 × CH_3), 70.6 (2 × CH_2), 110.3 (2 × CH_2), 119.7 (2 × CH), 122.4 (2 × CH), 125.3 (CH), 125.4 (2 × CH), 126.2 (2 × CH), 127.6 (2 × C), 128.8 (CH), 136.0 (2 × CH), 137.5 (2 × C),139.8 (2 × C), 153.6 (2 × C), 158.0 (2 × C). HRMS [ESI], m/z calcd for $C_{28}H_{24}N_2O_2Na$: $[M+Na]^+$ 443.1735: found 443.1722.

1,3-Bis-(5-chloro-8-quinolyloxymethyl)benzene ***4c*** White solid, Mp 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (4H, s), 6.88 (2H, d J = 8.4 Hz), 7.34–7.39 (3H, m), 7.43–7.46 (2H, m), 7.52–7.56 (2H, m), 7.62 (1H, s), 8.52 (2H, d J = 8.4 Hz), 8.99 (2H, d J = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.5 (2 × CH_2), 109.6 (2 × CH), 122.2 (2 × CH), 122.3 (2 × C), 125.5 (CH), 126.1 (2 ×CH), 126.6 (2 × CH), 126.9 (2 × C), 129.0 (CH), 132.7 (2 × CH), 136.9 (2 × C), 140.7 (2 × C), 149.6 (2 × CH), 153.1 (2 × C). HRMS [ESI], m/z calcd for $C_{26}H_{18}Cl_2N_2O_2Na$: $[M+Na]^+$ 483.0643: found 483.0654.

1,4-Bis-(8-quinolyl)oxymethyl)benzene ***5a*** White solid, Mp 122–123 °C; R_f (1% MeOH–$CHCl_3$) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (4H, s), 7.00–7.05 (2H, m), 7.33–7.37 (4H, m), 7.40–7.47 (2H, m), 7.52 (4H, s), 8.12 (2H, dd J = 1.5, 8.4 Hz), 8.95–8.97 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.1 (2 × CH_2), 109.6 (2 × CH), 119.6 (2 × CH), 121.3 (2 × CH), 126.3 (2 × CH), 127.1 (4 × CH), 129.1 (2 × C), 135.5 (2 × CH), 136.3 (2 × CH), 140.1 (2 × C), 149.0 (2 × CH), 153.9 (2 × C). HRMS [ESI], m/z calcd for $C_{26}H_{20}N_2O_2Na$: $[M+Na]^+$ 415.1422: found 415.1413.

1,4-Bis-(2-methyl-8-quinolyloxymethyl)benzene ***5b*** White solid, Mp 118–120 °C; R_f (1% MeOH–$CHCl_3$) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (6H, s), 5.42 (4H, s), 6.99 (2H, dd J = 1.5, 5.7 Hz), 7.25–7.34 (6H, m), 7.49 (4H, s), 8.01 (2H, d J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (2 × CH_3), 71.1 (2 × CH_2), 111.0 (2 × CH), 120.3 (2 × CH), 122.9 (2 × CH), 126.0 (2 × CH), 127.6 (4 × CH), 128.1 (2 × C), 136.5 (2 × CH), 137.1 (2 × C), 140.4 (2 × CH), 154.2 (2 × CH), 158.5 (2 × CH). HRMS [ESI], m/z calcd for $C_{28}H_{24}N_2O_2Na$: $[M+Na]^+$ 443.1735; found: 443.1713.

1,4-Bis-(5-chloro-8-quinolyloxymethyl)benzene ***5c*** White solid, Mp 141–143 °C; R_f (1% MeOH–$CHCl_3$) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (4H, s), 6.92 (2H, d J = 8.4 Hz), 7.42 (2H, d J = 8.4 Hz), 7.50–7.56 (6H, m), 8.51 (2H, dd J = 8.7 1.5, Hz), 8.99–9.01 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.1 (2 × CH_2), 110.2 (2 × CH), 122.7 (2 × CH), 122.9 (2 × C), 126.7 (2 × CH), 127.5 (2 × C), 127.9 (4 × CH), 133.4 (2 × CH), 136.8 (2 × C), 141.4 (2 × C), 150.2 (2 × CH), 153.8 (2 × C). HRMS [ESI], m/z calcd for $C_{26}H_{18}Cl_2N_2O_2Na$: $[M+Na]^+$ 482.0643; found: 482.0632.

2,3-Bis-(8-quinolyloxymethyl)napthaline ***6a*** White solid, Mp 172–173 °C; R_f (1% MeOH–$CHCl_3$) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (4H, s), 7.15–7.18 (2H, m), 7.26–7.37 (4H, m), 7.39–7.46 (4H, m), 7.79–7.82 (2H, m), 8.05 (2H, s), 8.08–8.11 (2H, m), 8.93–8.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.5 (2 × CH_2), 110.0 (2 × CH), 119.8 (2 × CH), 121.4 (2 × CH), 126.2 (2 × CH), 126.4 (2 × CH), 127.6 (2 × CH), 128.0 (2 × CH), 129.3 (2 × C), 132.5 (2 × C), 132.8 (2 × C), 135.7 (2 × CH), 140.4 (2 × C), 149.2 (2 × C), 154.0 (2 × C). HRMS [ESI], m/z calcd for $C_{30}H_{22}N_2O_2Na$: $[M+Na]^+$ 464.1579: found 464.1590.

2,3-Bis-(2-methyl-8-quinolyloxymethyl)napthaline ***6b*** White solid, Mp 170–171 °C; R_f (1% MeOH–$CHCl_3$) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (6H, s), 5.81 (4H, s), 7.12 (2H, d J = 7.2 Hz), 7.20 (2H, d J = 8.1 Hz), 7.25–7.30 (4H, m), 7.43–7.46 (2H, m), 7.79–7.82 (2H, m), 7.97 (2H, d J = 9.4 Hz), 8.08 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (2 × CH_3), 69.7 (2 × CH_2), 110.5 (2 × CH), 119.7 (2 × CH), 122.4 (2 × CH), 125.4 (2 × CH), 126.0 (2 × CH), 127.5 (2 × CH), 127.5 (2 × C), 127.7 (2 × CH), 132.68 (2 × C), 132.72 (2 × C), 135.9 (2 × CH), 140.0 (2 × C), 153.6 (2 × C), 158.0 (2 × C). HRMS [ESI], m/z calcd for $C_{32}H_{26}N_2O_2Na$: $[M+Na]^+$ 493.1892: found 493.1851.

2,3-Bis-(5-chloro-8-quinolyloxymethyl)napthaline ***6c*** White solid, Mp 178–180 °C; R_f (1% MeOH-$CHCl_3$) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (4H, s), 7.11–7.14 (2H, m), 6.96 (2H, d J = 8.1 Hz), 7.16 (2H, d J = 8.4 Hz), 7.46–7.54 (4H, m), 7.80–7.83 (2H, m), 8.00 (2H, s), 8.44–8.47 (2H, m), 8.92–8.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.4 (2 × CH_2), 119.7 (2 × CH), 122.1 (2 × CH), 125.9 (2 × CH), 126.5 (2 × CH), 126.7 (2 × C), 127.7 (2 × CH), 128.7 (2 × CH), 132.2 (2 × C), 132.7 (2 × CH), 132.9 (2 × C), 140.6 (2 × C), 149.4 (2 × CH), 150.1 (2 × C), 153.3 (2 × C). HRMS [ESI], m/z calcd for $C_{30}H_{20}Cl_2N_2O_2Na$: $[M+Na]^+$ 533.0799: found 533.0769.

2,3-Bis-(8-quinolyloxymethyl)quinoxaline ***7a*** White solid, Mp 190–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (4H, s), 7.04–7.11 (4H, m), 7.15–7.17 (2H, m), 7.35–7.39 (2H, m), 7.79–7.82 (2H, m), 8.08 (2H, d J = 8.4 Hz), 8.15–8.18 (2H, m), 8.86–8.87 (2H, m); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 71.2 (2 × CH_2), 109.7 (2 × CH), 119.9 (2 × CH), 121.3 (2 × CH), 126.0 (2 × CH), 128.8 (2 × CH), 129.0 (2 × C), 130.2 (2 × CH), 135.7 (2 × CH), 139.8 (2 × C), 140.9 (2 × C), 148.8 (2 × CH), 150.9 (2 × C), 153.6 (2 × C). HRMS [ESI], m/z calcd for $C_{28}H_{20}N_4O_2Na$: $[M+Na]^+$ 467.1584; found: 467.1543.

2,3-Bis-(2-methyl-8-quinolyloxymethyl)quinoxaline ***7b*** White solid, Mp 188–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (6H, s), 6.05 (4H, s), 7.12–7.13 (4H, m), 7.16–7.20 (2H, m), 7.24 (2H, bs) 7.79–7.82 (2H, m), 7.91 (2H, d J = 8.4 Hz), 8.17–8.21 (2H, m); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 25.2 (2 × CH_3), 71.2 (2 × CH_2), 110.0 (2 × CH), 119.8 (2 × CH), 122.2 (2 × CH), 125.0 (2 × CH), 127.2 (2 × C), 128.8 (2 × CH), 130.1 (2 × CH), 135.8 (2 × CH), 139.4 (2 × C), 140.8 (2 × C), 151.1 (2 × C), 153.1 (2 × C), 157.8 (2 × C). HRMS [ESI], m/z for $C_{30}H_{24}N_4O_2Na$: $[M+H]^+$ 495.1797; found: 495.1805.

2,3-Bis-(5-chloro-8-quinolyloxymethyl)quinoxaline ***7c*** White solid, Mp 201–203 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (4H, s), 6.75 (2H, d $J = 8.4$ Hz), 6.88 (2H, d $J = 8.4$ Hz), 7.44–7.49 (2H, m), 7.80–7.83 (2H, m), 8.12–8.15 (2H, m), 8.35–8.38 (2H, m), 8.82–8.84 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.5 (2 × CH_2), 109.3 (2 × CH), 122.1 (2 × CH), 122.3 (2 × C), 125.4 (2 × CH), 126.3 (2 × C), 129.1 (2 × CH), 130.4 (2 × CH), 132.6 (2 × CH), 140.2 (2 × C), 141.2 (2 × C), 149.2 (2 × CH), 150.8 (2 × C), 153.1 (2 × C). HRMS [ESI], m/z calcd for $C_{28}H_{18}Cl_2N_4O_2Na$: $[M+Na]^+$ 535.0704; found: 535.0685.

Pharmacological studies

Materials and methods

Microorganisms

The microorganisms used in this study consisted of eight strains of bacteria: *Staphylococcus aureus* 29737, *Shigella dysenteriae* 15, *Micrococcus luteus* ATCC 9341, *Escherichia coli* 319, *Bacillus pumilus 11778*, *Pseudomonas aeruginosa* 71, *Vibrio cholerae* 759, *Klebsiella pneumoniae* J/I/4 *and 4 fungi*: *Aspergillus niger*, *Candida albicans*, *Candida tropicalis*, and *Cryptococcus neoformans.* All the strains were clinical isolates from human beings. The strains were identified using Barrow and Feltham's method (Barrow and Feltham 1993) and were obtained from Division of Microbiology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India. The bacterial strains were grown in Mueller–Hinton Agar (Merck India Ltd.) at 37 °C for 24 h while the fungi were grown on Sabouraud dextrose agar at 28 °C for 3–5 days.

Preparation of inoculums

The desired bacteria and fungi were cultured in Mueller–Hinton Broth (MHB) and Sabouraud dextrose broth (SDB) at 37 °C for 24 h and at 28 °C for 72 h, respectively. The microorganism suspension was prepared by matching a 0.5 McFarland standard. (McFarland 1907).

Drug solution

All the test samples were dissolved in aqueous DMSO (up to 4%) to get the concentration of 1 mg/ml to be used as stock solution for the screening of their antimicrobial activity.

Determination of MIC

The antimicrobial activities of the test drugs were evaluated by finding the MIC as follows: MIC was determined by agar dilution and broth dilution methods. (Chattopadhyay *et al.*, 2002) For broth dilution assay, 0.1 ml standardized suspension of bacteria (2×10^6 cfu/ml) was added to Mueller–Hinton broth containing test drug at a concentration of 1–1000 μg/ml with appropriate antibiotic control and incubated at 37 °C overnight for bacteria.

For agar dilution assay, previously prepared drug dilutions of the test drug, with appropriate antibiotic control, were prepared in Mueller–Hinton Agar and Sabouraud dextrose agar. The mixtures were added into sterile petri-dishes after completely mixing. A loop of each microorganism standardized suspension (2×10^6 cfu/spot for bacteria and, 2×10^5 spores/spot for fungi) was inoculated on prepared agar plates by drawing a stripe. The inoculated plates were then incubated at 37 °C for 24 h for bacteria and at 28 °C for 96 h for fungi. The experiment was repeated thrice.

The lowest concentration required to inhibit the growth of microorganism, i.e., the concentration at which no microorganism colony or <5 colonies were visible within 19–38 h was considered as the MIC (Wang *et al.*, 2006).

Evaluation of zone of inhibition

Qualitative antimicrobial property of test samples was evaluated by disk diffusion method, as per NCCLS protocol (NCCLS 1993). For sensitivity testing 0.1 ml of bacterial suspension (2×10^6 cfu/ml) and 0.1 ml of fungal spore suspension (2×10^5 spores/ml) were transferred to freshly prepared Mueller–Hinton agar plates and Sabouraud dextrose plates. A sterile bent glass rod was used to spread the suspension to achieve uniform growth. Then sterile paper disks (5 mm diameter) impregnated into different drug concentrations were placed aseptically on sensitivity plates. The plates were then incubated at 37 °C overnight for bacteria and at 28 °C for 96 h for fungi. The sensitivity was recorded by measuring the clear zone of inhibition on agar surface around the disks.

Determination of the killing rate

The quantitative antimicrobial activities of the tested compounds were determined by using viable cell count

experiments (Rhim *et al.*, 2009). For this purpose the suspension of microorganism was diluted by sterile distilled water up to 2×10^6 cfu/ml. In each of the test tubes containing drug samples (**3c**, **6c**) at their MIC ranges, 1 ml of bacterial suspension (2×10^6 cfu/ml) was added; another test tube containing suspension of microorganism without drug sample was taken as control. All of them were placed into a Mueller–Hinton broth and incubated at 37 °C with continuous shaking on platform shaker at 200 rpm.

Aliquots of 1 ml sample withdrawn at 0, 1, 2, 4, 6, 8 h till 48 h and were spread on nutrient agar plates and incubated at 37 °C overnight. The numbers of colonies were counted and reduction in plate colonies was calculated by comparing with control plates.

Scanning electron microscopic (SEM) study

The suspension of bacteria (2×10^6 cfu/ml) was divided into two halves after 12 h incubation in Mueller–Hinton broth at 37 °C. The drug sample solution was added to the one portion of the bacteria suspension so that MIC concentration is achieved, and the other portion was left untreated for control. After 24 h incubation, the bacteria cells from both test tubes were harvested by centrifugation, and washed twice with sterile nutrient broth. The bacteria cells obtained by centrifugation were fixed in 3% (v/v) glutaraldehyde buffered with 0.1 M sodium phosphate buffer (pH 7.2) for an hour at room temperature and dehydrated in a graded alcohol series. The specimens were dried and mounted on stubs using double-sided carbon tape. A thin layer of gold was then coated using a microscope sputter coater for 1 min at 20 mA. The coated sample was then examined in a JEOL-JSM 6360 Scanning Electron Microscope (Russell and Hugo, 1994).

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