Synthesis, anticorrosion, antibacterial, and antifungal activity of new amphiphilic compounds possessing quinazolin-4(3*H*)-one scaffold

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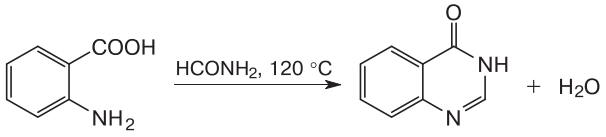
For the first time, quinazolin-4(3*H*)-one-based cationic surfactants were prepared and fully characterized by IR and NMR spectroscopic techniques and elemental analysis. Some of their physicochemical properties, such as density, critical micelle concentration, surface tension, effectiveness in surface tension reduction, Gibbs free energy of micellization, foam and emulsion stability, and anticorrosion activity were determined. Antibacterial and antifungal activities of the synthesized compounds were investigated. *N,N*-Dimethyl-*N*-{2-[(2-methyl-4-oxoquinazolin-3(4*H*)-yl)amino]-2-oxoethyl}tetradecan-1-aminium chloride (**4a**) showed the highest antibacterial activity against five human pathogens. Antifungal activity against *Candida albicans* was shown only by surfactant **4a**.

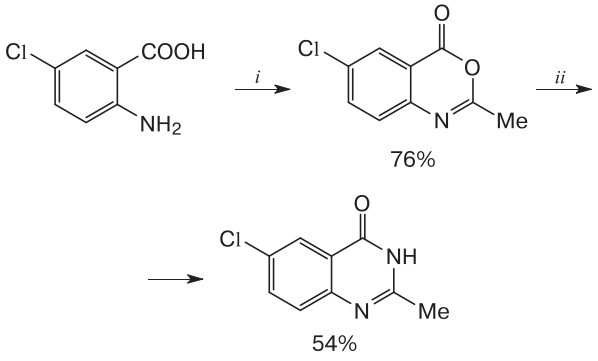
Key words: anticorrosion activity, antibacterial activity, antifungal activity, heterocyclic surfactants, quinazolin-4(3*H*)-one, Gibbs free energy of micellization.

Nitrogen-containing heterocyclic compounds are an important class of organic compounds due to their diverse biological activities. The representatives of this class of heterocycles are the derivatives of quinazolin-4(3*H*)-one (also known as 4-oxo-quinazoline).[1] The name quinazoline, earlier known as benzo-1,3-diazine, was first proposed for this bicyclic compound by Weddige.[2] The facile synthesis of quinazolin-4(3*H*)-one by heating the starting material anthranilic acid with excess formamide in an open vessel at 120 °C is known as Niementowski reaction[3] (Scheme 1). Another procedure employed by Jiang and co-workers[4] involved the treatment of 5-chloroanthranilic acid with acetic anhydride to afford the benzoxazinone in 76% yield. Subsequent stirring of benzoxazinone with ammonium acetate at an elevated temperature afforded 6-chloro-2-methylquinazolin-4(3*H*)-one in 54% yield (Scheme 2). Similar reaction was also performed in good yields by Nouira *et al*.[5] under microwave irradiation conditions (200 W) over 10 min at 200 °C. These findings clearly indicate that significant advancement has been made in recent years in the synthesis of these heterocyclic compounds.

Scheme 1



Scheme 2



i. Ac_2O, reflux; *ii*. NH_4OAc, 150 °C, 0.5 h.

Heterocyclic compounds with quinazolin-4(3*H*)-one skeleton garnered great interest because of their biological activities, such as anticancer,[6—8] antimicrobial,[9—11] antifungal,[12] anti-inflammatory,[11,13—15] analgesic,[13—16] anticonvulsant,[16,17] antitumor,[18,19] antiviral,[20,21] and antibacterial[13,14,22,23] properties.

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In recent years, studies have been carried out on the synthesis of quinazolin-4(3*H*)-one derivatives containing long alkyl chain. These quinazolinone derivatives have found important applications in industrial areas as metallic corrosion inhibitors[24,25] and in pharmacology as antimicrobial agents.[26—29] In long chain quinazolinone derivatives having antimicrobial activity, the long carbon chain is bound to the quinazoline carbon atom located between two nitrogen atoms.

In the present study, quinazolin-4-one-derived cationic surfactants were synthesized and characterized using Fourier transform infrared (FT-IR) and NMR spectroscopy. Antibacterial and antifungal activities of the synthesized compounds were investigated.

Experimental

Reagents and solvents were purchased from Merck (Germany). A Thermo Nicolet 6700 FT-IR spectrometer (USA) was used for acquisition of the attenuated total reflectance FT-IR spectra. The NMR spectra were measured on an A600a Agilent DD2 600 MHz NMR spectrometer (USA) in DMSO-d_6 at working frequencies of 600 (^{1}H) and 150 MHz (^{13}C). The elemental analyzes were performed with a LECO CHNS-932 elemental analyzer (USA).

2-Methyl-4*H*-benzo[*d*][3,1]oxazin-4-one (**1a**) used as the starting material in the synthesis was purchased from Merck. 2-Phenyl-4*H*-benzo[*d*][3,1]oxazin-4-one (**1b**) was synthesized from anthranilic acid as previously described.[20] Synthesis of 3-amino-2-methylquinazolin-4(3*H*)-one (**2a**) and 3-amino-2-phenylquinazolin-4(3*H*)-one (**2b**) were carried out according to the earlier developed method.[14,20]

Synthesis of compounds 3a,b. A solution of 1 equiv. of amine **2a** or **2b** and 1.5 equiv. of chloroacetyl chloride in DMF was refluxed for 6 h. After completion of the reaction, the reaction mixture was cooled, treated with ice-cold water, the precipitate obtained was collected by filtration, washed with water, dried, and crystallized from ethanol to give 2-chloro-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide (**3a**) and 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide (**3b**). Physicochemical and spectral properties of compounds **3a** and **3b** are in agreement with those published earlier.[30]

Synthesis of surfactants 4a,b, and 5a,b (general procedure). A mixture of 1 equiv. of compound **3a** or **3b**, 1 equiv. of long-chain tertiary amine and EtOH were heated at 120 °C for 48 h. After completion of the reaction, the mixture was cooled and the excess of solvent was removed under reduced pressure. The residue was washed three times with diethyl ether—petroleum ether (1 : 3).[31] A yellow waxy products were obtained quantitatively in sufficient purity.

***N,N*-Dimethyl-*N*-{2-[(2-methyl-4-oxoquinazolin-3(4*H*)-yl)amino]-2-oxoethyl}tetradecan-1-aminium chloride (4a).** Yellow waxy solid. Yield 93%. Found (%): C, 65.69; H, 9.24; N, 11.31. $C_{27}H_{45}ClN_4O_2$. Calculated (%): C, 65.76; H, 9.20; N, 11.36. IR, ν/cm^{-1}: 3250 (N—H, amide); 1672 (C=O, cyclic amide); 1608 (C=O, amide). ^{1}H NMR, δ: 8.08 (d, 1 H, Ar, J = 8.0 Hz); 7.84 (t, 1 H, Ar, J = 7.7 Hz); 7.76 (t, 1 H, Ar, J = 7.7 Hz); 7.58 (d, 1 H, Ar, J = 7.8 Hz); 5.80 (s, 1 H, HNC=O); 3.08 (s, 2 H, C(O)C$\underline{H}_2$N$^+$); 2.92 (t, 2 H, CH$_2$C$\underline{H}_2$N$^+$, J = 7.7 Hz); 2.66 (s, 6 H, N$^+$(CH$_3$)$_2$); 2.56 (s, 3 H, CCH$_3$); 1.78 (quint, 2 H, C$\underline{H}_2$CH$_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.59 (quint, 2 H, C$\underline{H}_2$CH$_2$-CH$_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.24—1.20 (m, 20 H, CH$_2$); 0.83 (t, 3 H, CH$_2$C$\underline{H}_3$), J = 7.0 Hz). ^{13}C NMR, δ 165.39 (HNC=O); 160.45 (C=O in quinazolinone); 155.93 (N=$\underline{C}$(CH$_3$)N); 147.05 (1 C, Ar); 134.35 (1 C, Ar); 127.06 (1 C, Ar); 126.36 (1 C, Ar); 126.30 (1 C, Ar); 120.18 (1 C, Ar); 65.34 (C(O)$\underline{C}$H$_2$N$^+$(CH$_3$)$_2$); 64.23 ((CH$_3$)$_2$N$^+$$\underline{C}H_2CH_2$); 56.89 (C$\underline{C}H_3$); 50.47 (C(O)CH$_2N^+$-($\underline{C}H_3$)$_2$); 31.74—22.34 (11 C, CH$_2$); 21.62 ($\underline{C}H_2CH_3$); 14.38 (CH$_2$$\underline{C}H_3$).

***N,N*-Dimethyl-*N*-{2-oxo-2-[(4-oxo-2-phenylquinazolin-3(4*H*)-yl)amino]ethyl}tetradecan-1-aminium chloride (4b).** Yellow waxy solid. Yield 98%. Found (%): C, 69.29; H, 8.48; N, 9.99. $C_{32}H_{47}ClN_4O_2$. Calculated (%): C, 69.23; H, 8.53; N, 10.09. IR, ν/cm^{-1}: 3210 (N—H, amide), 3100 (C$_{Ar}$—H); 1686 (C=O, cyclic amide); 1591 (C=O, amide). ^{1}H NMR, δ: 8.12 (d, 1 H, Ar, J = 7.8 Hz); 7.91 (t, 2 H, Ar, J = 7.7 Hz); 7.76 (d, 2 H, H$_o$ in Ph, J = 7.8 Hz); 7.69 (d, 1 H, Ar, J = 7.8 Hz); 7.62 (t, 1 H, Ar, J = 7.7 Hz); 7.54 (t, 2 H, H$_m$ in Ph, J = 7.7 Hz); 7.47 (t, 1 H, H$_p$ in Ph, J = 7.7 Hz); 5.65 (s, 1 H, HNC=O); 3.25 (s, 2 H, C(O)CH$_2$N$^+$); 2.93 (t, 2 H, CH$_2$C$\underline{H}_2$N$^+$, J = 7.7 Hz); 2.48 (s, 6 H, CH$_3$N$^+$CH$_3$); 1.75 (quint, 2 H, C$\underline{H}_2$CH$_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.51 (quint, 2 H, C$\underline{H}_2$CH$_2$CH$_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.26—1.17 (m, 20 H, CH$_2$), 0.83 (t, 3 H, CH$_2$C$\underline{H}_3$, J = 7.0 Hz). ^{13}C NMR, δ: 164.91 (HNC=O); 159.33 (C=O in quinazolinone); 155.90 (N=$\underline{C}$(Ph)N); 146.95 (1 C, Ar); 139.69 (1 C, Ar); 129.31 (1 C, C$_p$ in Ph); 128.99 (2 C, C$_m$ in Ph); 128.42 (1 C, C$_{ipso}$ in Ph); 128.19 (2 C, C$_o$ in Ph); 128.01 (1 C, Ar); 127.41 (1 C, Ar); 126.99 (1 C, Ar); 121.10 (1 C, Ar); 65.05 (C(O)-$\underline{C}$H$_2$N$^+$(CH$_3$)$_2$); 60.99 ((CH$_3$)$_2$N$^+$$\underline{C}H_2CH_2$); 51.74 (C(O)-CH$_2N^+$($\underline{C}H_3$)$_2$); 31.73—26.08 (11 C, $\underline{C}$H$_2$); 22.53 ($\underline{C}$H$_2$CH$_3$); 14.39 (CH$_2$$\underline{C}H_3$).

***N,N*-Dimethyl-*N*-{2-[(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-amino]-2-oxoethyl}hexadecan-1-aminium chloride (5a).** Yellow waxy solid. Yield 96%. Found (%): C, 66.79; H, 9.51; N, 10.69. $C_{29}H_{49}ClN_4O_2$. Calculated (%): C, 66.83; H, 9.48; N, 10.75. IR, ν_{max}/cm^{-1}: 3245 (N—H, amide); 1672 (C=O, cyclic amide); 1608 (C=O, amide). ^{1}H NMR, δ: 8.08 (d, 1 H, Ar, J = 8.0 Hz); 7.84 (t, 1 H, Ar, J = 7.7 Hz); 7.75 (t, 1 H, Ar, J = 7.7 Hz); 7.58 (d, 1 H, Ar, J = 7.8 Hz); 5.80 (s, 1 H, HNC=O); 3.09 (s, 2 H, C(O)C$\underline{H}_2$N$^+$); 2.92 (t, 2 H, CH$_2$C$\underline{H}_2$N$^+$, J = 7.7 Hz); 2.66 (s, 6 H, N$^+$(CH$_3$)$_2$); 2.57 (s, 3 H, CCH$_3$); 1.78 (quint, 2 H, C$\underline{H}_2$C$\underline{H}_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.60 (quint, 2 H, C$\underline{H}_2$-CH$_2$CH$_2$N$^+$(CH$_3$)$_2$, J = 7.0 Hz); 1.26—1.18 (m, 24 H, CH$_2$); 0.83 (t, 3 H, CH$_2$C$\underline{H}_3$, J = 7.0 Hz). ^{13}C NMR, δ: 165.50 (HNC=O); 160.45 (C=O in quinazolinone); 155.92 (N=$\underline{C}$-(CH$_3$)N); 147.05 (1 C, Ar); 134.34 (1 C, Ar); 127.06 (1 C, Ar); 126.35 (1 C, Ar); 126.30 (1 C, Ar); 120.18 (1 C, Ar); 65.35 (C(O)-$\underline{C}$H$_2$N$^+$(CH$_3$)$_2$); 64.19 ((CH$_3$)$_2$N$^+$$\underline{C}H_2CH_2$); 56.87 (C$\underline{C}H_3$); 50.49 (C(O)CH$_2N^+$($\underline{C}H_3$)$_2$); 31.74—24.09 (13 C, CH$_2$), 22.53 ($\underline{C}H_2CH_3$); 14.38 (CH$_2$$\underline{C}H_3$).

***N,N*-Dimethyl-*N*-{2-oxo-2-[(4-oxo-2-phenylquinazolin-3(4*H*)-yl)amino]ethyl}hexadecan-1-aminium chloride (5b).** Yellow waxy solid. Yield 98%. Found (%): C, 70.10; H, 8.74; N, 9.55. $C_{34}H_{51}ClN_4O_2$. Calculated (%): C, 70.02; H, 8.81; N, 9.61. IR, ν_{max}/cm^{-1}: 3225 (N—H, amide); 3110 (C$_{Ar}$—H); 1687 (C=O, cyclic amide); 1591 (C=O, amide). ^{1}H NMR, δ: 8.16 (d, 1 H, Ar, J =7.8 Hz); 7.91 (d, 2 H, H$_o$ in Ph, J = 7.8 Hz); 7.73 (t, 1 H, Ar, J = 7.7 Hz); 7.60 (d, 2 H, Ar, J = 7.8 Hz); 7.53 (t, 2 H, H$_m$ in Ph, J = 7.7 Hz); 7.45 (t, 1 H, H$_p$ in Ph, J = 7.7 Hz); 5.69 (s, 1 H, HNC=O); 3.28 (s, 2 H, O=CC$\underline{H}_2$N$^+$); 2.91 (t, 2 H,

$CH_2C\underline{H}_2N^+$, J = 7.7 Hz); 2.48 (s, 6 H, $N^+(C\underline{H}_3)_2$); 1.77 (quint, 2 H, $C\underline{H}_2CH_2N^+(CH_3)_2$, J = 7.0 Hz); 1.51 (quint, 2 H, $C\underline{H}_2CH_2CH_2N^+(CH_3)_2$, J = 7.0 Hz); 1.25—1.15 (m, 24 H, CH_2); 0.81 (t, 3 H, CH_2CH_3, J = 7.0 Hz). ^{13}C NMR, δ: 164.83 (HNC=O); 159.28 (C=O in quinazolinone); 155.92 (N=$\underline{C}$(Ph)N); 146.98 (1 C, Ar); 139.85 (1 C, Ar); 129.26 (1 C, C_p in Ph); 129.07 (2 C, C_m in Ph); 128.93 (1 C, C_{ipso} in Ph); 128.33 (2 C, C_o in Ph); 128.13 (1 C, Ar); 127.40 (1 C, Ar); 126.95 (1 C, Ar); 121.13 (1 C, Ar); 65.07 ($C(O)\underline{C}H_2N^+(CH_3)_2$); 61.09 ($(CH_3)_2N^+$-$\underline{C}H_2CH_2$); 51.95 ($C(O)CH_2N^+(\underline{C}H_3)_2$); 31.75—26.18 (13 C, CH_2); 22.55 ($\underline{C}H_2CH_2$); 14.35 ($CH_2\underline{C}H_3$).

Critical micelle concentration (CMC) the surfactants was determined using the conductometric method. Conductivity measurements were performed using a Thermo Scientific ORION 3 STAR digital conductometer (USA). The specific conductivity of the surfactant was measured by the step-by-step dilution-extraction method. The CMC values were estimated from the break point on the curve of electric conductivity *versus* surfactant concentration.

Surface tension at the CMC. Surface tensions of the aqueous solutions of the synthesized cationic surfactants was measured by the capillary rise method.[32,33] A capillary used for the measurement is Na-heparinized micro hematocrit tube (NRIS, Soda Lime glass, d = 1.0 mm, l = 75 mm). The related values were measured at 20 °C.

Foam properties. The following two parameters of the foam properties were examined: the foam height and the foam stability. The foam height was measured as previously described.[34] Twenty-five mL of an aqueous solution of the surfactant at the CMC was shaken vigorously for 10 s in a calibrated 100-mL glass cylinder with a glass stopper. The length and diameter of the cylinder used in the foam height measurements at 20 °C were 18 and 2.2 cm, respectively. The solution was allowed to stand for 30 s and then the foam height was measured. The foam stability was determined by measurement of changes in the foam volume after shaking the aqueous surfactant solutions (10 mL) at the CMC for 30 s in the same glass cylinder used for foam height measurements. Foam experiments were carried out at 20 °C using ultrapure water (resistivity of 18.2 MΩ cm) which was prepared using an Elga Purelab Option Q water purification system. The measurement of foam volume of the surfactant solutions was performed as described below. The glass cylinder was sealed and vigorously shaken for 30 s and the initial measurement was made immediately. The subsequent measurements of the foam volumes were done 5 and 30 min after shaking.[35] The measurements were repeated twice for each surfactant.

Emulsion stability was determined by mixing the aqueous solution of the surfactants with the mineral oil in a 100-mL graduated cylinder with a plastic stopper. A 10 mL of aqueous surfactant solution at the CMC was poured into a 100-mL cylinder containing 10 mL of the mineral oil. The glass cylinder was closed with stopper. The mixture was shaken by turning vigorously the glass cylinder up and down for 30 s at constant speed and then the time for the separation of 9 mL of clean surfactant solution was noted.[36]

Anticorrosion activity test in 1.0 *M* HCl solution. The corrosion test in acidic medium was performed using the coupons made of cold-rolled low-carbon steel according to DIN EN 10130[37] that contains 0.07% C, 0.35% Mn, 0.015% P, and 0.015% S. Metal coupons cut into rectangular shapes of 0.1×2.2×5.0 cm in thickness, width, and length, respectively, were immersed in 15% HCl before the immersion test. Then the coupons were slightly polished with paper tissue, washed with deionized water, and dipped in acetone. The corrosion tests of compounds **4a**,**b** and **5a**,**b** were performed in 1.0 *M* HCl solution prepared from the concentrated HCl (37%, Merck). The solutions of cationic surfactants with the concentration of 10, 25, 50, 100, and 250 ppm prepared by dissolving the test surfactant in the acid solution, were poured into 150-mL sealed glass bottles. The coupons were immersed in these solutions without stirring for 24 h at room temperature. After the test time, the coupons were removed, rinsed with water, wiped with paper tissues, washed with acetone, and dried to a constant weight in an oven at 40 °C. Control tests were performed in the same way without the inhibitors.

Antibacterial activity was tested on the human pathogens extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ATCC 35218), methicillin-resistant *Staphylococcus aureus* (clinical isolate), *Klebsiella pneumoniae* (ATCC 700603), *Pseudomonas aeruginosa* (ATCC 27853), and *Enterococcus faecalis* (ATCC 291212). For the disk-diffusion assay, bacteria were grown in nutrient broth (NB; LabM Limited, UK) at 37 °C for 24 h diluted in sterile saline (0.85% NaCl) solution to McFarland 0.5, and spread on nutrient agar (NA; LabM Limited, UK) plates. The surfactants (2 μg) dissolved in DMSO were added on blank disks (Oxoid, UK) placed on bacteria. Erythromycin (15 μg) and chloramphenicol (30 μg) disks (Oxoid, UK) were used as standard antibiotics, and DMSO was used as a negative control. The plates were incubated overnight at 37 °C, and the diameters of zones without bacterial growth around the disks were measured. All samples were assayed in triplicates.

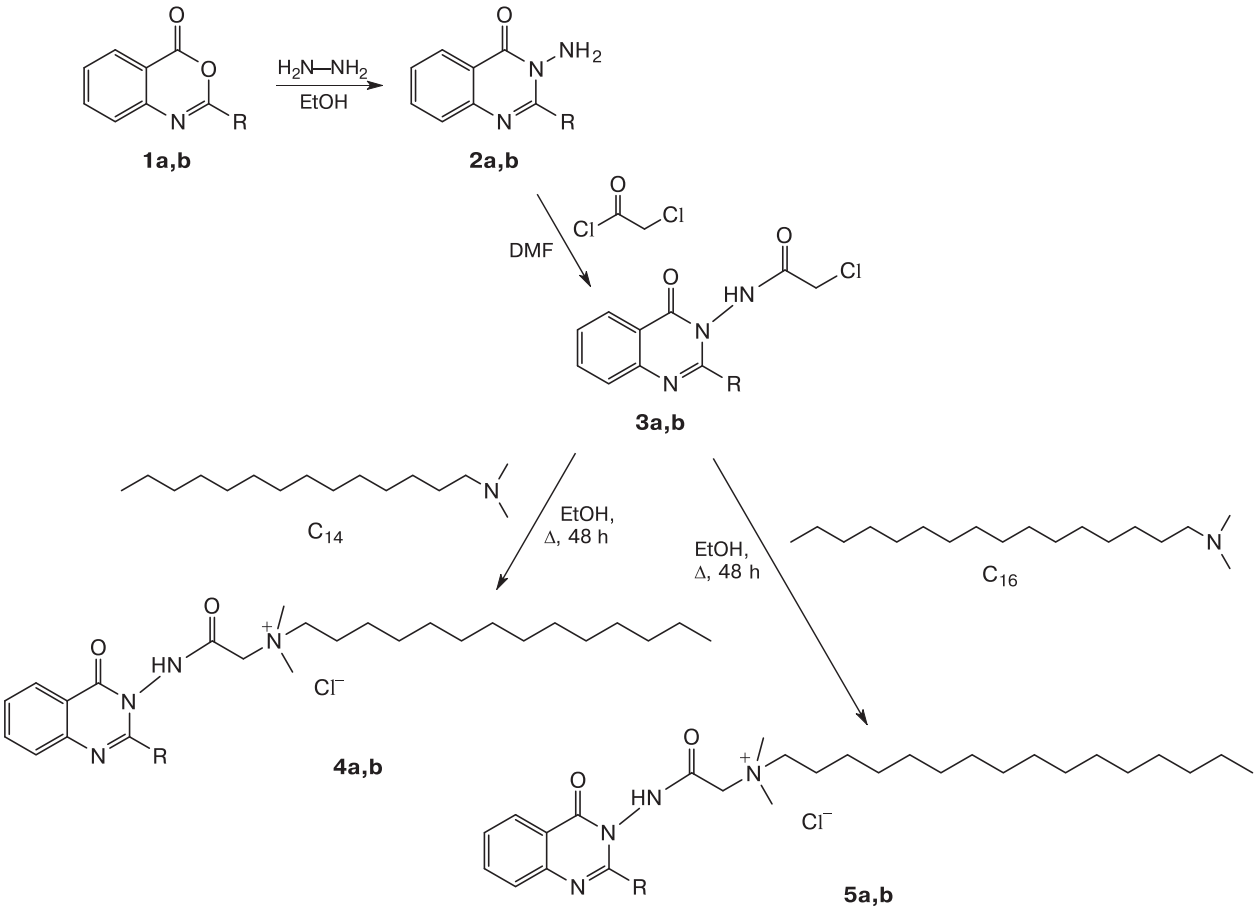
The minimum inhibitory concentration (MIC) assay was performed using the same human pathogens grown in NB and diluted to McFarland 0.5. Suspensions of bacteria (200 μL) of were added to the wells of a 96-well plate, and serial two-fold dilution of the surfactants from 20 to 0.625 μg mL^{-1} concentration was performed. The plates were covered and incubated at 37 °C for 24 h. The optical density (OD) of the bacterial growth was measured at 630 nm using RT-2100C microplate reader (Rayto, China). All samples were assayed in duplicates. The lowest concentration providing an 80% growth reduction as compared to negative control (DMSO) was accepted as MIC.[38]

Antifungal activity was tested on *Candida albicans* (ATCC 10231). The culture of *C. albicans* was prepared in potato dextrose broth (PDB; Merck, Germany) at 37 °C for 24 h. The culture was diluted to McFarland 0.5 using sterile saline solution, and spread on potato dextrose agar (PDA; Merck, Germany) plates. The surfactants (2 μg) of dissolved in DMSO were added on blank disks placed on *C. albicans* cells. The plates were incubated overnight at 37 °C, and the diameters of growth inhibition zones around the disks were measured. Fluconazole (25 μg) was used as a standard. All samples were assayed in triplicates.

Results and Discussion

Synthesis of cationic surfactants was performed in three steps (Scheme 3). In the first two steps, known *N*-amino-substituted methyl- and phenylquinazolinones **2a**,**b** and the corresponding chloroacetamide derivatives **3a**,**b** were synthesized. In the third step, compounds **3a**,**b** were reacted with tertiary amine containing 14 carbon atoms in the long chain to give compounds **4a**,**b**. The reaction of

Scheme 3



R = Me (**a**), Ph (**b**)

compounds **3a**,**b** with the tertiary amine compound containing 16 carbon atoms in the alkyl chain under similar conditions gave compounds **5a**,**b**. Newly synthesized cationic surfactants (**4a,b** and **5a,b**) were characterized using FT-IR and ^{1}H and ^{13}C NMR spectroscopy. FT-IR and ^{1}H and ^{13}C NMR spectra of compound **4a** are shown in Fig. 1 as an example.

Physicochemical properties of surfactants. Various physicochemical parameters like density (ρ), critical micelle concentration, surface tension at the CMC (γ_{CMC}), surface effectiveness (π_{CMC}) and Gibbs free energy of micellization (ΔG_{mic}) were measured and/or calculated for cationic surfactants (Table 1).

The CMC of the cationic surfactants were determined by conductivity measurements. The CMC values were determined from the break points in the plots of specific conductivity *versus* surfactant concentration[39] (Fig. 2). As seen in Fig. 2, upon an increase in concentration conductivity also showed a linear increase and the concentration at which the slope was changed were taken as CMC for

Table 1. Physicochemical properties of the cationic surfactants **4a,b** and **5b**

Compound[a]	$\rho^{b,c}$/g mL^{-1}	CMC^{b} · 10^{-5}/mol L^{-1}	$\gamma_{CMC}{}^{b}$/dyn cm^{-1}	π_{CMC}/dyn cm^{-1}	ΔG_{mic}/kJ mol^{-1}
4a	1.0280	24.04	32.74	40.06	−20.30
4b	1.0283	6.56	30.23	42.57	−23.46
5b	1.1212	9.29	32.96	39.84	−22.62

[a] No measurements for compound **5a** were performed.
[b] At 20 °C.
[c] At CMC of the surfactant.

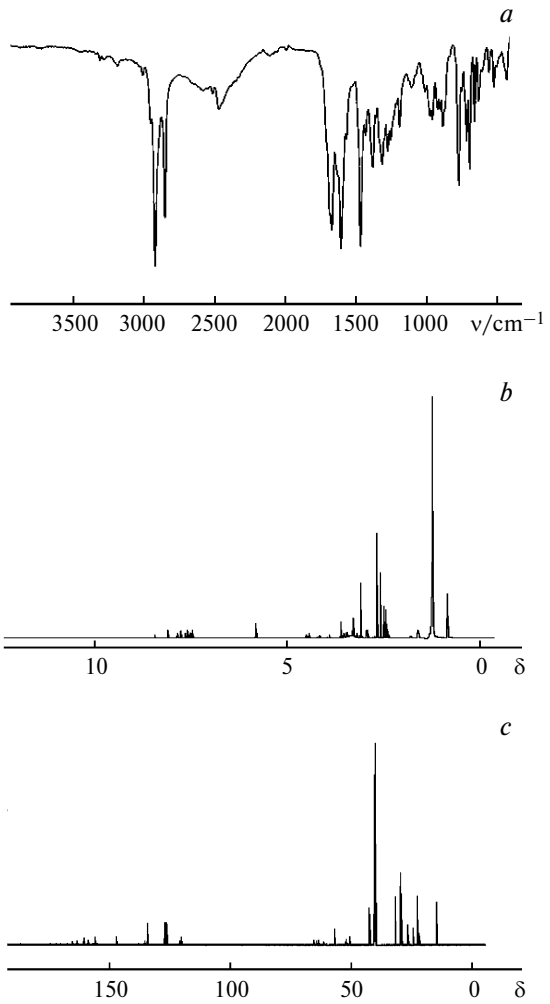


Fig. 1. The FT-IR (*a*), ^{1}H (*b*) and ^{13}C NMR (*c*) spectra of compound **4a**.

the synthesized surfactants. The CMC were found to be equal $24.04 \cdot 10^{-5}$ mol L^{-1} for compound **4a**, and $6.56 \cdot 10^{-5}$ mol L^{-1} for compound **4b**, $9.29 \cdot 10^{-5}$ mol L^{-1} for compound **5b**. From these results, it can be concluded that the micelles of these cationic surfactants are formed at low concentrations. Comparing compounds **4a** and **4b**, it was found that the CMC of compound **4b** was lower than that of compound **4a**. It is notable that surfactants **4a** and **4b** contain the same carbon chains. The only difference between compounds **4a** and **4b** is that compound **4a** has a methyl group in the quinazolinone ring and compound **4b** has a phenyl ring. The phenyl-substituted compound **4b** is more hydrophobic than the methyl-substituted compound **4a**. Note that an increase in the hydrophobic character of the cationic surfactant leads to a decrease in the critical micelle concentration. The phenyl group acts as a hydrophobic unit since it is commonly admitted that its contribution to the CMC is roughly equivalent to

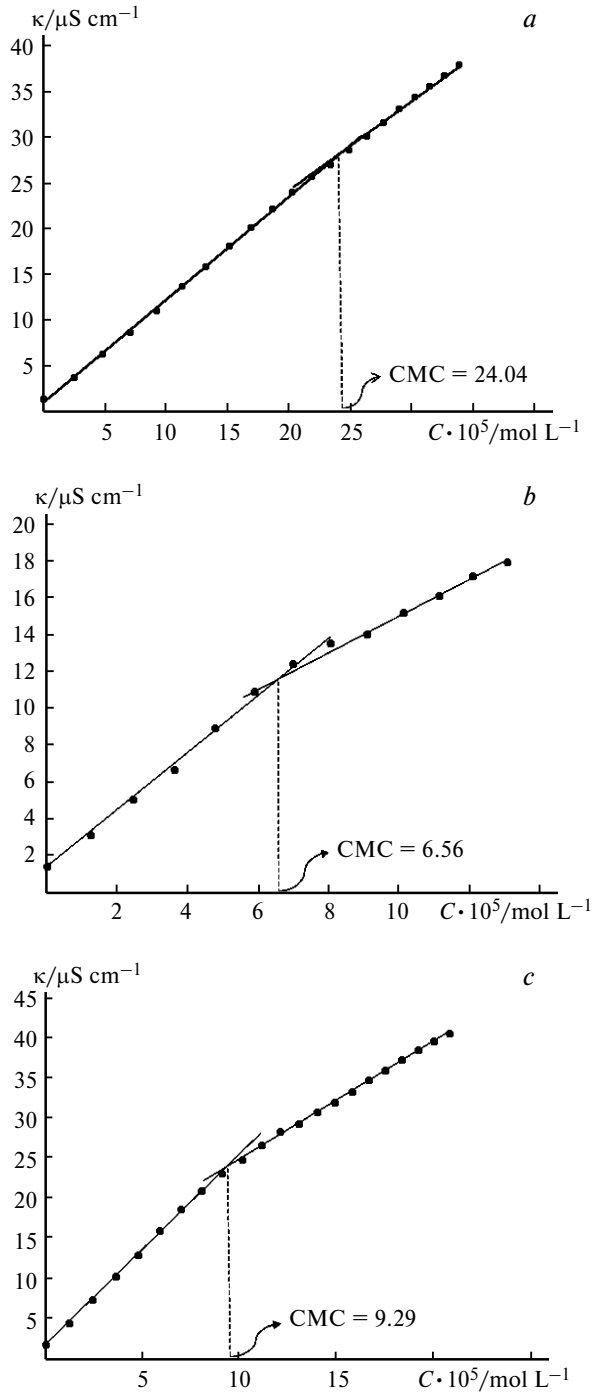


Fig. 2. Conductivity as a function of surfactant concentration for the determination of critical micelle concentration of compounds **4a** (*a*), **4b** (*b*), and **5b** (*c*).

3.5 methylene groups.[40] In addition, the CMC value of compound **5b** was slightly higher than that of compound **4b**, although the critical micelle concentrations were close to each other. Compound **5b** has a longer carbon chain and should have a lower CMC value than compound **4b**.

We can explain this result as follows: the hydrophobic chains in the surfactant molecule has little effect on CMC when it reaches a certain length. This is because of the tangling of the excessively long hydrophobic chains hindered effective micellization and the long hydrophobic chains also weaken the water solubility of surfactant. This diminished the effect of the chain elongation.[41]

At the same time, the CMC of the surfactants reflects the changes in the Gibbs free energy of micellization (ΔG_{mic}). As the critical micelle concentration of the surfactant decreases, the tendency of the substance to form micelles increases. The ΔG_{mic} value, which is calculated by Eq. (1), proves this information.

$$\Delta G_{mic}\ (\text{J mol}^{-1}) = RT \ln(\text{CMC}), \qquad (1)$$

where R — is the ideal gas constant, T is temperature (K).

The ΔG_{mic} become more negative by increasing hydrophobic character of the surfactant.[42] As shown in Table 1, compound **4b** having the lowest CMC value is more prone to form the micelles than compound **4a**, since its hydrophobic character is higher.

Surface tensions (γ_{CMC}) of the synthesized surfactants at the CMC were determined according to the capillary rise method.[32,33] The surface tensions were measured to evaluate the surface activity of the aqueous solution of cationic surfactant at the CMC. Among the synthesized cationic surface-active compounds, the lowest surface tension at the CMC was found for compound **4b**. This indicates that compound **4b** exhibits better surface activity properties than the others.

The effectiveness in surface tension reduction (π_{CMC}) is also an important parameter to evaluate the surface activity of the aqueous solution of surfactant at the CMC. This parameter is closely related to the surface tension at the CMC and reflects the reduction in surface pressure attained at the CMC. [31] The π_{CMC} value can be calculated from the equation

$$\pi_{CMC} = \gamma_0 - \gamma_{CMC}, \qquad (2)$$

where γ_0 is the surface tension of the solvent (for water at 20 °C, γ_0 = 72.8 dyn cm^{-1}), γ_{CMC} is the surface tension of solution at the CMC.

The calculated π_{CMC} values or compounds **4a**, **4b**, and **5b** were 40.06, 42.57, and 39.84 dyn cm^{-1}, respectively. These results indicate that the synthesized cationic surfactants have the potential to reduce the surface tension in the aqueous system. It is known that the activity of the surfactant increases with the increasing the π_{CMC} values. Therefore, compound **4b** with the highest π_{CMC} value will show better surface activity than the other surfactants.

The foam properties of the synthesized cationic surfactants were investigated as foam height, foamability and foam stability (Table 2). These parameters of the surfactants were studied in water at two concentrations, namely, at the CMC and concentration higher than CMC ($1 \cdot 10^{-3}$ mol L^{-1}). The initial foam volume (V_0, mL) was reported as the foamability. The initial foam height strongly depends on the concentration of the surfactants. At higher concentration the greater foam volumes were obtained.[35] When we compared the foam heights and foaming abilities of the synthesized compounds, it appeared that the formation of foam by compounds **4b** and **5b** with the phenyl group at the quinazolinone ring is reduced. This can be explained in terms of the micellar stability. In conventional surfactants the very stable micelles cause poor foaming ability, because rupture of micelles is too slow to generate foam bubbles.[43] Consequently, the foaming ability will be

Table 2. Foam height (h), foam volume (V), and foam stability of the cationic surfactants **4a,b** and **5a,b**

Surfactant	h/mm[a]		V/mL[a]						Foam stability (%)			
	$1.0 \cdot 10^{-3}$ mol L^{-1}	CMC	initial		after 5 min		after 30 min		$1.0 \cdot 10^{-3}$ mol L^{-1}		CMC	
			V_0[b]	V_0[c]	V_1[b]	V_1[c]	V_2[b]	V_2[c]	after 5 min[d]	after 30 min[e]	after 5 min[f]	after 30 min[g]
4a	148	40	52	9	45	7	35	6	86.5	67.3	77.8	66.7
4b	63	5	20	2	15	1.5	14	1	75.0	70.0	75.0	50.0
5a	120	—[h]	60	—[h]	32	—[h]	28	—[h]	53.3	46.7	—[h]	—[h]
5b	58	—[h]	20	—[h]	15	—[h]	13	—[h]	75.0	65.0	—[h]	—[h]

[a] At 20 °C.
[b] Foam volume measured at the surfactant concentration of $1 \cdot 10^{-3}$ mol L^{-1}.
[c] Foam volume measured at CMC.
[d] $[V_1^b/V_0^b] \cdot 100\%$.
[e] $[V_2^b/V_0^b] \cdot 100\%$.
[f] $[V_1^c/V_0^c] \cdot 100\%$.
[g] $[V_2^c/V_0^c] \cdot 100\%$.
[h] No foam formation.

poor due to the micellar stability. Thus, it can be concluded that the micelle stability for the surface-active agents **4b** and **5b** with the phenyl group at the quinazolinone ring is higher than that of compounds **4a** and **5a** with the methyl group at the heterocycle. The CMC and ΔG_{mic} values measured for the surfactants supported this result. In addition, due to very low h and V_0 values, the surfactants **4b** and **5b** are promising for oilfield wastewater treatment.[44] Moreover, as seen in Table 2, there were no significant changes between the foam stability measured 5 and 30 min after foam formation. This means that the synthesized surfactants form permanent foam.

The emulsion stabilities of the synthesized cationic surfactants were determined as the time required for the breakdown of the emulsion formed between surfactant solution and mineral oil. The emulsion stability of the synthesized surfactants was also studied at two concentrations (at the CMC and $1.0 \cdot 10^{-3}$ mol L^{-1}) (Table 3). As seen from Table 3, emulsion stability directly depends on the concentration. The emulsion stability of the surfactants at the concentration of $1.0 \cdot 10^{-3}$ mol L^{-1} was significantly higher than that at the CMC. In addition, emulsion stability was lower for the surfactants with the phenyl group at the quinazolinone ring. As was mentioned above, the phenyl-substituted compounds **4b** and **5b** are more hydrophobic than the methyl-substituted compounds **4a** and **5a**. Higher hydrophobic character leads to lower water solubility of the surfactant.[41] In this way, the emulsion ability is reduced. However, a comparison of the stability of emulsion formed by compounds **4a** to **5a** and **4b** to **5b** showed that compounds **5a** and **5b** with the longer alkyl groups produced more stable emulsions than compounds **4a** and **4b** with shorter alkyl group. The reason for this situation is the longer hydrophobic chain produces more viscous solutions. The viscous solutions mitigate the chances of diffusion. This is leading to increment in emulsion stability.[45]

Corrosion inhibition tests. Corrosion-inhibiting efficiencies of the synthesized cationic surfactants were explored in the acidic medium (1.0 *M* HCl) using weight loss measurements. Results of the corrosion inhibition efficiency for the synthesized cationic surfactants at different concentrations are given in Table 4. Corrosion inhibition capabilities of the synthesized compounds at different concentrations are given as percentage inhibition efficiencies (IE), which were calculated using equation

$$IE = [(W_0 - W)/W_0] \cdot 100\ (\%), \quad (3)$$

where W_0 is the weight loss of the coupon in the absence of an inhibitor, W is the weight loss of the coupon in the same environment in the presence of an inhibitor.

Table 3. Emulsion stabilities of the cationic surfactants **4a,b** and **5a,b** at 20 °C

Surfactant	Emulsion stability/s	
	$1.0 \cdot 10^{-3}$ mol L^{-1}	CMC
4a	1636	382
4b	1185	23
5a	1792	—
5b	1468	42

Table 4. Corrosion inhibition efficiencies (IE (%)) calculated for different concentrations of surfactants **4a**,**b** and **5a**,**b** in 1.0 *M* HCl for 24 h at room temperature

Surfactant	EI (%) at concentration of surfactant/ppm				
	10	25	50	100	250
4a	95.45	96.44	96.24	96.63	96.34
4b	94.95	95.84	96.04	96.83	96.73
5a	96.24	96.34	95.84	95.94	96.04
5b	90.40	93.86	95.34	95.05	95.74

As seen in Table 4, the synthesized surfactants exhibited excellent corrosion inhibition efficiency in 1.0 *M* HCl solution over 24 h at room temperature. At selected concentrations, all surfactants exhibited similar inhibitory properties and it was observed that the inhibition efficiency increased slightly with increasing the inhibitor concentration.

In the general structure of the synthesized cationic surfactants, there is a long carbon chain that will keep the water molecules away from the metal surface, the heteroatoms (N and O) that will provide adsorption to the metal surface, and the quinazoline ring. In addition, a positively charged nitrogen atom will provide solubility in acidic aqueous medium. The possible inhibition mechanism for the compounds is shown in Fig. 3. As seen in Fig. 3, N and O heteroatoms are chemically adsorbed to the metal surface and the positively charged nitrogen atom is adsorbed by electrostatic interaction.

Antimicrobial activity. Quinazoline and quinazolinone compounds attract attention in medicinal chemistry due to their wide range of biological activities such as antibacterial, antifungal, antiviral, and antimalarial properties.[46] In our study, the antibacterial activity of the synthesized quinazoline derivatives **4a**,**b** and **5a**,**b** was evaluated *via* disk-diffusion assay. According to the diameters of growth inhibition zones, compound **4a** showed the highest antibacterial activity against all tested human pathogens (Table 5). Compound **4a** was found to be more effective against *E. coli* and *E. faecalis* than erythromycin and chloramphenicol. Compounds **4a**,**b** and **5a**,**b** were also tested for their antifungal activity against *C. albicans* using disk-diffusion assay, and only compound **4a** showed 12-mm inhibition zone, while fluconazole provided 26-mm inhibition zone.

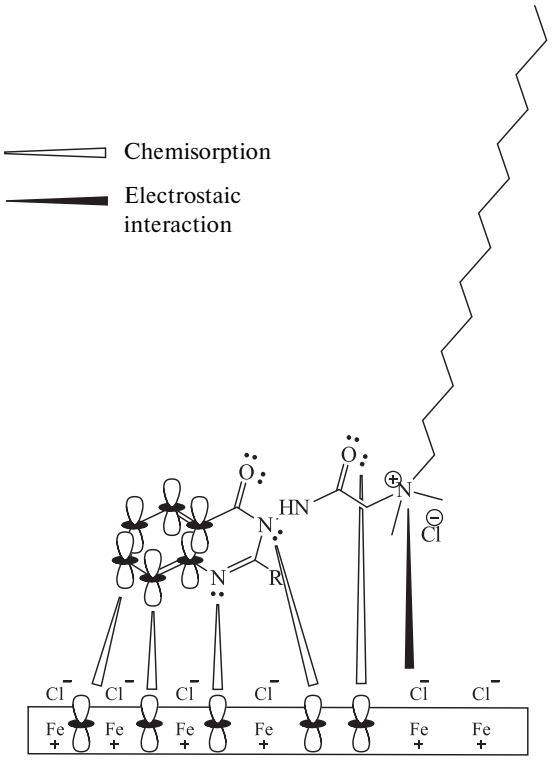


Fig. 3. The possible corrosion inhibition mechanism for the cationic surfactants.

The minimum inhibitory concentration (MIC) assay gave results only for 2-methyl-substituted compounds **4a** and **5a** (Table 6) because 2-phenyl-substituted compounds **4b** and **5b** produced self-turbidity therefore the optical density of the bacteria could not be determined. The MIC values of compound **4a** against all tested human pathogens were found to be lower than those of compound **5a**. Compound **4a** possessed the lowest MIC against ESBL-producing *E. coli* and the highest MIC against *K. pneumoniae*. Additionally, this cationic surfactant showed lower MIC values than chloramphenicol against *K. pneumoniae*, *E. coli*, and *E. faecalis* as well as the same MIC values against *P. aeruginosa* and *S. aureus*. Compound **5a** showed higher MIC values against *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* than chloramphenicol, whereas these substances possessed the same MIC values against *E. coli* and *E. faecalis*.

Our findings showed that surfactants **4a**,**b** containing 14 carbon atoms in the alkyl chain were more effective than compounds **5a**,**b** with 16 carbon atoms, and the 2-methyl-substituted derivatives **4a**, **5a** showed higher activity than 2-phenyl-substituted derivatives **4b**, **5b**. In contrast to the reported data that methyl group at position 2 is essential for antimicrobial activity of quinazolinone compounds[46] and substitution in phenyl ring with methoxy and methyl groups increased the antibacterial activity of the 3-pyrimidine-1-yl quinazoline derivatives,[47] the

Table 5. Antibacterial activity of compounds **4a**,**b** and **5a**,**b** against human pathogens

Compound	Mean diameter of the growth inhibition zone/mm				
	K. pneumoniae	*E. coli*	*E. faecalis*	*P. aeruginosa*	*S. aureus*
4a	10.0±0.6	16.0±0	13.7±0.6	15.0±0.6	15.0±0.6
4b	—[c]	14.7±0.6	12.7±0.6	12.7±0.6	12.3±0.6
5a	—[c]	9.0±0.6	9.0±0.6	9.0±0.6	—[c]
5b	—[c]	—[c]	9.0±0.6	—[c]	—[c]
Chloramphenicol	8.0±0.6	8.0±0.6	9.0±0.6	26.7±0.6	22.3±0.6
Erythromycin	10.0±0.6	12.7±0.6	11.7±0.6	25.0±0.6	25.0±0.6
DMSO[b]	—[c]	—[c]	—[c]	—[c]	—[c]

[a] Compounds **4a**,**b** and **5a**,**b** were tested in amount of 2 μg, erythromycin was used in amount of 15 μg and chloramphenicol was used in amount of 30 μg.
[b] DMSO was added in amount of 10 μL.
[c] No inhibition.

Table 6. Minimum inhibitory concentrations (μg mL^{-1}) of compounds **4b** and **5b** against human pathogens

Compound[a]	*K. pneumoniae*	*E. coli*	*E. faecalis*	*P. aeruginosa*	*S. aureus*
4a	5	1.25	2.5	2.5	2.5
5a	20	10	10	10	20
Chloramphenicol	10	10	10	2.5	2.5
DMSO	—[b]	—[b]	—[b]	—[b]	—[b]

[a] No measurements for compounds **4b** and **5b** were performed.
[b] No inhibition.

higher antibacterial activity of 2-phenyl quinazolines than 2-methyl quinazolines was found by Abd-Elhakeem and A. M. Elsayed[48] and Saravanan and coworkers.[49] Moreover, it have been shown that introduction of the methoxy group in the quinazoline skeleton enhances the antibacterial activity.[50,51] It also should be noted that replacement of the phenyl group of 2-phenyl-3-substituted quinazolin-4(3*H*)-ones with the methyl increases the analgesic and anti-inflammatory activities.[14]

In summary, four new 4-oxoquinazoline cationic surfactants were synthesized as potential antibacterial and antifungal agents. Some physicochemical and anticorrosion properties on mild steel in acidic medium of the synthesized cationic surfactants were investigated. All the cationic surfactants demonstrated efficient corrosion inhibition on mild steel in the 1.0 *M* HCl medium by adsorption on the metal surface. Among the synthesized cationic surfactants, compound **4a** showed the highest antibacterial activity against tested human pathogens. This cationic surfactant was the only compound that was active in the antifungal activity test. Therefore, compound **4a** is promising for the development of antimicrobial surfaces.

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