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Synthesis and Antibacterial Evaluation of Three Quaternary Ammonium Surfactants Based on Isatin

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In present study, several isatin-derived quaternary ammonium surfactants with different carbon chain lengths were designed and synthesized. They were synthesized by alkylation of indoline-2,3-dione with various dibromo-alkanes, then quaternization with trimethylamine. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) and mass spectroscopy were employed to examine their chemical structures. Further, the critical micelle concentrations (CMC) value of surfactants synthesized was determined in an aqueous solution using electrical conductivity. The synthesized surfactants had CMC ranging from 0.01 to 0.012 mol/L. The antibacterial activity of the titer compounds (**3a-3c**) was evaluated against Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), as well as Gram-positive bacteria (*Staphylococcus aureus*). The surfactant with a long hydrocarbon chain (12 carbons) showed activity against all bacteria tested (minimum inhibitory concentration = 1.25-2.5 mg/mL), whereas those with a short hydrocarbon chain proved to be inactive.

Keywords: Isatin, Surfactants, Quaternary ammonium compounds, Antibacterial activity, CMC.

INTRODUCTION

The scarcity of new antibacterial drugs and the increasing bacterial resistance to antimicrobial agents are crucial issues for drug development and research [1]. The exploration of heterocyclic scaffolds with medical privileges is one of the areas of drug discovery [2]. The isatin (1*H*-indole-2,3-dione) compound is ubiquitous, and its derivatives provide several activities such as anti-inflammatory [3], antibacterial [4,5], anti-depressant [6], anti-tubercular [7], anti-viral [8], analgesic [9], antifungal [10] and anticorrosive properties [11,12].

As a "privileged building block", almost all the isatin part sites can be reacted, the N-1, C-3 and C-5 positions are the main chemical variation areas [10]. Besides, various isatin-based molecules, such as indirubin and semaxanib have been used in clinical or research trials to treat diverse diseases [2]. The wide range of biological activities associated with a wide range of structural modifications and their successful application in clinical practice has inspired more researchers to study isatin based more structurally diverse derivatives [2]. In this case, one major problem that prevents large-scale bioassays is the low solubility of the target compound in biocompatible solvents, primarily water. One possible solution is to introduce a salt group into the molecule of an isatin derivative [13].

In addition, many non-antibiotic chemical fragments have been developed and utilized as alternative antibacterial agents. These include phosphonium salts, biguanides, iodine, triazoles, and quaternary ammonium compounds (QACs), the latter being considered more effective due to the positive charge of their structure [14]. The antibacterial property of positively charged QACs may be accounted for their electrostatic interaction with the negatively charged phospholipid membranes of bacteria [15]. Moreover, it has been suggested that QACs may interact with the phospholipid components of the cellular membrane,

causing membrane distortion under osmotic pressure and leading to protoplast dissolution [14]. The QACs can be a lipid or surfactant consisting of a long hydrocarbon chain linked to a positively charged nitrogenous head group. When QACs are used as surfactants, especially in nanoformulations for targeted and specific drug delivery, the strong electrostatic interaction between these molecules and the bacterial cell wall is advantageous [14]. The self-association capacity of surfactants molecules let acquire a great interest in various fields such as technological, chemical, and biological areas as pharmaceuticals [16], cosmetics [17], textiles [18], mining [19,20], paper manufacturing [21], the synthesis of micro-materials [22], membrane mimetics [23], biocides and germicides [24,25]. This type of molecule leads to micellization due to its amphiphilic character [26]. In polar solvents such as water, the hydrophilic head of surfactants is positioned at the micelle-solvent interface, while the micelle core consists of the hydrophobic part [27]. The critical micelle concentration CMC is the concentration that indicates stable micelle formation [26]. The CMC can be determined in different ways and is the concentration at which a sudden change in several physical properties is observed, such as osmotic pressure, surface tension, light scattering, electrical conductivity, solubilization, interfacial tension and turbidity [26].

For the above reasons, the main purpose of this work is to prepare a series of quaternary ammonium surfactants based on isatin with different lengths of lipophilic alkyl chains (C3, C6 and C12). We prepared three compounds through the *N*-alkylation reaction of 1*H*-indole-2,3-dione and then quaternized the resulting product with tertiary amines. We have chosen trimethylamine as an amination agent for their effectiveness efficacy compared with other amines as tripropylamine and trimethylamine [28]. The chemical structure of the cationic surfactants were characterized by nuclear magnetic resonance ^{1}H & ^{13}C and mass spectrometry, the electrical conductometric method was used for determining the critical micelle concentration of surfactants synthesized. Furthermore, antibacterial activity of those cationic surfactants was assessed against different bacteria.

EXPERIMENTAL

Melting points of compounds synthesized were determined by Digital Melting Point Apparatus, HRMS spectra were acquired on Orbitrap LTQ XL (Thermo-Fisher) at a resolution 30,000 from *m/z* 150-2000. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker 300 spectrometer in $CDCl_3$ or D_2O as solvent chemical shifts are expressed in ppm (δ) and tetramethylsilane as a reference.

Synthesis of compounds (2a-2c): A mixture of ^{1}H-indole-2,3-dione (1.0 g, 6.796 mmol) and 1,12-dibromododecane (**1c**) (2.68 g, 8.167 mmol) in DMF (40 mL) in the presence of K_2CO_3 (1.4 g, 10.13 mmol) and tetra-*n*-butylammonium bromide (0.24 g, 0.745 mmol) as a catalyst was stirred for 48 h at room temperature. After filtering of the mixture the solvent was removed under vacuum the crude reaction product was purified by column chromatography. Orange product was obtained with 78% yield.

Synthesis of compounds 3a-3c: The quaternization reaction of compound **2c** was performed in a 250 mL two-necked flask fastened to a reflux condenser. Compound **2c** (1g; 2.536 mmol) was dissolved into 40 mL of ethanol and then trimethylamine (31-35% w/w) (3.3 mL; 12.98 mmol) was added dropwise. The reaction was stirred for 72 h at room temperature and then the solvent was removed under vacuum and the crude product residual was purified by solubilization in the minimum amount of ethanol and then precipitated in the ether; the precipitate orange product obtained with 96% was characterized by NMR and mass spectroscopy.

1-(3-Bromopropyl)indoline-2,3-dione (2a): Yield 62%; m.p: 183 ºC; HRMS (EI) *m/z* (%): calculated for $C_{11}H_{10}O_2NBr$ + H^+ 267.9968, found 267.9929. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.63 (m, 2H, CH_{Ar}); 7.16 (td, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.5 Hz, $^{4}J_{H\text{-}H}$ = 0.7Hz), 7.04 (dd, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.8 Hz, $^{4}J_{H\text{-}H}$ = 0.6 Hz), 3.92 (t, 2H, NCH_2, $^{3}J_{H\text{-}H}$ = 7.05 Hz), 3.5 (t, 2H, CH_2Br, $^{3}J_{H\text{-}H}$ = 6.3 Hz), 2.3 (qn, 2H, $CH_2CH_2CH_2Br$, $^{3}J_{H\text{-}H}$ = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 183.12 (C=O); 158.37 (N-C=O); 150.71, 117.63 (Cq); 138.54, 125.63, 123.93, 110.08 (CH_{Ar}); 38.84, 30.31, 30.05 (CH_2).

1-(6-Bromohexyl)indoline-2,3-dione (2b): Yield 70 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.58 (m, 2H, CH_{Ar}), 7.1 (m, 1H, CH_{Ar}), 6.91 (d, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.8 Hz), 3.72 (t, 2H, NCH_2, $^{3}J_{H\text{-}H}$ = 7.5 Hz); 3.37 (t, 2H, CH_2Br, $^{3}J_{H\text{-}H}$ = 6.6 Hz); 1.84 (qn, 2H, CH_2CH_2Br, $^{3}J_{H\text{-}H}$ = 6.9 Hz), 1.71 (qn, 2H, CH_2CH_2N, $^{3}J_{H\text{-}H}$= 7.5 Hz), 1.44 (m, 4H, (CH_2 $(CH_2)_2CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 158.17 (N-C=O), 117.55, 150.92, (Cq), 110.19, 123.68, 125.41, 138.05, (CH_{Ar}), 26.03, 27.10, 27.69, 32.49, 33.73, 40.05 (CH_2).

1-(12-Bromododecyl)indoline-2,3-dione (2c): Yield: 78%, m.p: 61 ºC; HRMS (EI) *m/z* (%): calculated for $C_{20}H_{28}O_2NBr$ + H^+ 394.1376, found 394.1329. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.6 (m, 2H, CH_{Ar}), 7.1 (t, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.5 Hz); 6.9 (d, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 8.1 Hz), 3.7 (t, 2H, NCH_2, $^{3}J_{H\text{-}H}$ = 7.5 Hz), 3.4 (t, 2H, CH_2Br, $^{3}J_{H\text{-}H}$ = 6.9 Hz), 1.85 (q, 2H, CH_2CH_2Br, $^{3}J_{H\text{-}H}$ = 7,5Hz), 1.7 (q, 2H, CH_2CH_2N, $^{3}J_{H\text{-}H}$ = 7.5 Hz); 1.4 (m, 16H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 158.12 (N-C=O), 151.08, 117.59 (Cq), 138.32, 125.40, 123.58, 110.18 (CH_{Ar}), 40.26, 34.07, 32.81, 29.44, 29.42, 29.37, 29.19, 28.73, 28.14, 27.24, 26.87 (CH_2).

3-(2,3-Dioxoindolin-1-yl)-*N*,*N*,*N*-trimethylpropan-1-ammonium bromide (3a): Yield: 97%, m.p.: 240 ºC. HRMS (EI) *m/z* (%): calculated for $C_{14}H_{19}O_2N_2$ 247.1441; found 247.1407. ^{1}H NMR (D_2O, 300 MHz) δ ppm: 7.59 (td, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.8 Hz, $^{4}J_{H\text{-}H}$ = 1.2 Hz), 7.41 (dd, 1H, CH_{Ar}, $^{3}J_{H\text{-}H}$ = 7.5 Hz, $^{4}J_{H\text{-}H}$ = 0.9 Hz), 7.05 (m, 2H, CH_{Ar}), 3.72 (t, 2H, CH_2N, $^{3}J_{H\text{-}H}$ = 6.8 Hz), 3.4 (t, 2H, CH_2N^+, $^{3}J_{H\text{-}H}$ = 8.4 Hz), 3.05 (s, 9H, CH_3N^+), 2.15 (qn, 2H, CH_2CH_2N, $^{3}J_{H\text{-}H}$ = 7.6 Hz). ^{13}C NMR (D_2O, 75 MHz) δ ppm: 184.25 (C=O), 159.93 (N-C=O), 149.79, 117.30 (Cq), 139.41, 125.58, 124.62, 111.00 (CH_{Ar}), 63.77 (CH_2N^+), 53.10, 53.04, 52.98 (CH_3N^+), 36.94 (CH_2N), 20.96 (CH_2).

6-(2,3-Dioxoindolin-1-yl)-*N*,*N*,*N*-trimethylhexan-1-ammonium bromide (3b): Yield: 98%, m.p.: 177 ºC; HRMS (EI) *m/z* (%): calculated for $C_{17}H_{25}O_2N_2$ 289.1911; found 289.1865. ^{1}H NMR (D_2O, 300 MHz) δ ppm: 7.50 (td, 1H, CH_{Ar},

$^{3}J_{H-H}$ = 7.5 Hz, $^{4}J_{H-H}$ = 1.2 Hz), 7.30 (dd, 1H, CH_{Ar}, $^{3}J_{H-H}$ = 7.5 Hz, $^{4}J_{H-H}$ = 0.9 Hz), 6.95 (m, 2H, CH_{Ar}), 3.49 (t, 2H, CH_2N^+, $^{3}J_{H-H}$ = 6.9 Hz), 3.22 (m, 2H, CH_2N), 3.01 (s, 9H, CH_3N^+), 1.67 (m, 2H, $CH_2CH_2N^+$), 1.54 (qn, 2H, CH_2CH_2N), 1.29 (qn, 4H, CH_2). ^{13}C NMR (D_2O, 75 MHz) δ ppm: 184.63 (C=O), 159.47 (N-C=O), 116.99, 150.38 (Cq), 111.28, 124.40, 125.32, 139.38 (CH_{Ar}), 66.49 (CH_2N^+), 52.76, 52.81, 52.85 (CH_3N^+), 39.94 (CH_2N), 22.19, 25.06, 25.55, 26.19 (CH_2).

12-(2,3-Dioxoindolin-1-yl)-N,N,N-trimethyldodecan-1-ammonium bromide (3c): Yield: 96 %, m.p.: 171 ºC. HRMS (EI) *m/z* (%): calculated for $C_{23}H_{37}O_2N_2$ 373.2855; found 373.2794. ^{1}H NMR (D_2O, 300 MHz) δ ppm: 7.53 (t, 1H, CH_{Ar}, $^{3}J_{H-H}$ = 7.5 Hz); 7.26 (d, 1H, CH_{Ar}, $^{3}J_{H-H}$ = 7.2 Hz), 6.97 (t, 2H, CH_{Ar}, $^{3}J_{H-H}$ = 7.5 Hz), 3.5 (m, 2H, CH_2N^+), 3.27 (t, 2H, CH_2N, $^{3}J_{H-H}$ = 8.1 Hz), 3.08 (s, 9H, CH_3N^+), 1.63 (m, 2H, $CH_2CH_2N^+$), 1.42 (m, 2H, CH_2CH_2N), 1.08 (m, 16H, CH_2). ^{13}C NMR (D_2O, 75 MHz) δ ppm: 183.96 (C=O), 158.24 (N-C=O), 150.77, 117.01 (Cq), 139.37, 124.90, 123.97, 111.16 (CH_{Ar}), 53.01 (CH_3N^+), 66.47, 65.97, 61.76, 40.06, 29.45, 29.39, 29.15, 28.97, 27.13, 26.72, 26.00, 22.69 (CH_2).

Antibacterial activity: Three bacterial strains including two Gram-negative strains, namely *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) and one Gram-positive strain, which is *Staphylococcus aureus* (ATCC 29213). These bacteria were selected from the collection of the Microbial Biotechnology and Bioactive molecules Laboratory, Faculty of Sciences and Technologies, Fez, Morocco. Before use, strains were revivified by subcultures in Luria-Bertani (LB) plates at 37 ºC for 24 h.

Determination of minimum inhibitory concentration against bacteria: Minimum inhibitory concentration method was used to determine the lowest concentration inhibitory by preventing growth of microorganisms and also as a preliminary test for qualitative determination of antibacterial activity. The MIC values were determined in a 96-well microplate using the microdilution method according to Chraibi *et al*. [29] and to Fichtali *et al*. [30] with slight modifications. Briefly, a stock solution of each product was prepared in double-distilled water. Then, a serial dilution of the tested products ranging from 5 mg/mL to 0.0025 mg/mL in Mueller-Hinton Broth medium (MHB) was prepared, and in each well of the plate 50 µL of bacterial strain was added at a concentration of 10^6 CFU/mL. A well was considered as growth control (free drug control). Then, the plates were incubated at 37 ºC for 24 h. To assist in the determination of MIC, 10 µL of rezasurin was added to each well for 2 h, the MIC corresponds to the lowest concentration of the extract, which does not produce a change in rezasurin coloration and which corresponds to the absence of bacterial growth. Experiments were carried out in triplicate.

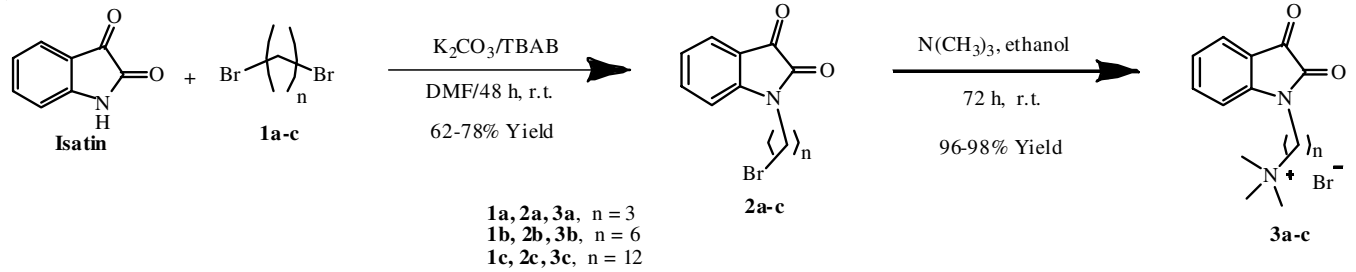
RESULTS AND DISCUSSION

Synthesis of surfactants isatin derivatives containing ammonium moiety: The surfactants derived from isatins with a quaternary ammonium moiety (**3a**-**3c**) were obtained in high yields by two subsequent steps as reported earlier (**Scheme-I**) [31-33]. The first step is an alkylation reaction of isatin by a dibromoalkane in DMF in the presence of K_2CO_3 as a base, tetra-n-butylammonium bromide (TBAB) as a catalyst to prepare *N*-alkylated isatin with bromide at the extremity. In second step, the synthesized compound **2a**-**2c** was converted to the corresponding surfactant by quaternization reaction with trimethylamine in ethanol at room temperature. The desired products **3a**-**3c** were obtained in 96-98% yield after purification by precipitation in diethyl ether. The surfactants were soluble in ethanol, methanol and water.

CMC determination: The critical micelle concentration (CMC) is the base characteristic of surfactants [34]. It is generally used in engineering applications and interface science to evaluate its ability to adsorb across the interface and form micelle assemblies [35]. The CMC of any surfactant can be determined experimentally by plotting the appropriate physical properties against the surfactant concentration [36]. The Phillips method [26,37,38] and the Williams method [29,39,40] are two data analysis methods that can be used to determine the CMC using conductivity plots. The first determines the CMC using the second derivative of the conductivity plot *versus* surfactant concentration, whereas the second uses the point where two linear fits of the surfactant concentration range below and above the CMC intersect. In the order to determine the critical micelle concentration (CMC) of the studied cationic surfactants, their conductivity were measured using a conductometer at room temperature. All measurements were performed in pure water for different concentrations of surfactants synthesized at pH 7.

Fig. 1 shows the electrical conductivity as a function of the concentration of the studied surfactants. There evidently exist breakpoint corresponding to the CMC in their plot, where the electrical conductivity of cationic surfactants solutions increase with surfactant concentration at different rates before and after the intersection point (CMC) in this plot.

The augmentation of electric conductivity in the function of surfactants concentration can be explained by the augmentation of number of free ions in the solution [41]. Above the breakpoint (CMC) in the slope, the rate of increase in the electrical conductivity is reduced by the reason of the binding



Scheme-I: Synthesis of surfactants isatin derivatives containing a quaternary ammonium moiety

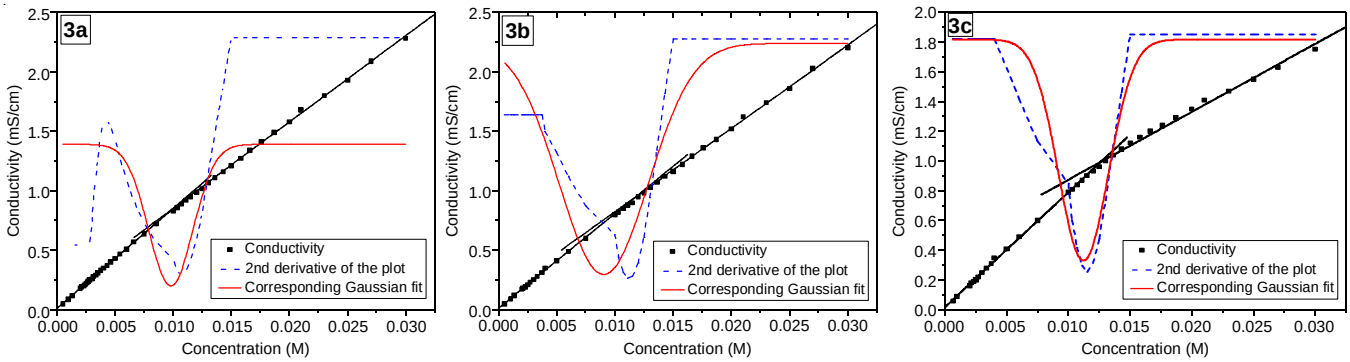


Fig. 1. Specific conductivity of studied surfactant **3a-c**, 25 °C

of some of the counter-ions of the cationic surfactant to the micelles [41,42]. The capability of transporting the charge decreases in the presence of aggregates. The CMCs value obtained at 25 ºC in aqueous solution was varied from 0.01 to 0.012 mol/L as shown in Fig. 1.

Antibacterial activity: The antibacterial activity of the synthesized compounds **3a**-**3c** was evaluated against three different bacterial strains *viz*. *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Staphylococcus aureus* (ATCC 29213). Screening was conducted using a microdilution method, which determines the minimum inhibitory concentration (MIC) [29,30,43].

Antimicrobial activity results are presented in Table-1, it was suggested that compound **3c** shows an effect against all strains tested Gram-positive and Gram-negative with MICs at 2.5, 1.25 and 1.25 mg/mL against *E. coli*, *S. aureus* and *P. aeruginosa*, respectively. However, the other two compounds **3a** and **3b** showed no effect against the three strains tested.

TABLE-1
ANTIMICROBIAL ACTIVITY RESULTS

Products	*E. coli*	*S. aureus*	*P. aeruginosa*
3a	–	–	–
3b	–	–	–
3c	2,5 mg/mL	1,25 mg/mL	1,25 mg/mL

The antibacterial properties of synthetic quaternary ammonium derived from isatin are indeed affected by the length of their alkyl chains; this result is very consistent with the previous findings in the literature [44-46]. This could be due to the long alkyl chain provides a hydrophobic segment compatible with the double layer of the bacterial outer cell wall [46]. Depending on the hydrophilicity or hydrophobicity of the surfactant, the increase alkyl chain length of the synthesized compound, allows penetration of the bacterial cell to perturb the membrane, like a balloon pierced by a needle, which enhanced the antibacterial activity of the compound [46,47].

The complete mechanism of the antibacterial effect of quaternary ammonium salts has not been fully understood. The common mechanism of these compounds is widely regarded as death by contact. A lipophilic long alkyl chain crosses the bacterial cell membrane by combining with the components of the cell wall, causing leakage of cytoplasmic material, autolysis and bacterial cell death [46]. This mechanism of contact killing, by destroying the cell wall, does not cause bacteria and microorganisms to develop resistance to these materials [48].

Conclusion

In this work, three isatin-based quaternary ammonium surfactants with different hydrocarbon chains were synthesized through a two-step reaction process through the alkylation and quaternization reactions. Their chemical structure was confirmed using ^{1}H NMR, ^{13}C NMR and mass spectrometry. The conductimetric technique was applied to measure the CMC of three cationic surfactants in water at room temperature. Their antibacterial activity has been tested against Gram-positive *Staphylococcus aureus* and Gram-negative *Pseudomonas* and *Escherichia coli* bacteria. Compound **3c** exhibited antibacterial activity against all three microorganisms tested, with MICs ranging from 1.25 to 1.5 mg/mL, however compounds **3a** and **3b** had no antibacterial activity. This result could be exploited to use our synthesized molecule in the formulation of a new antibacterial agents. Furthermore, medicinal uses for the drugs solubilization are also possible.

CONFLICT OF INTEREST

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

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