Synthesis, Surface Parameters, and Biodegradability of Water-soluble Surfactants for Various Applications

Refat El-Sayed¹,² *, Hawazin H Alotaibi¹ and Heba A Elhady¹,³

¹ Chemistry Department, College of Applied Sciences, Umm Al-Qura University, 21955Makkah, SAUDI ARABIA
² Chemistry Department, Faculty of Science, Benha University, EGYPT
³ Chemistry Department, Faculty of Science (Girl’s), Al-Azhar, University, Cairo, EGYPT

Abstract: The synthesis of water-soluble heterocyclic compounds was verified on the basis of nonionic surfactants for use as surface-active agents. Surface characteristics such as surface and interfacial tensions, cloud point, wetting time, emulsion stability, foaming height and foaming stability were measured for these surfactants in aqueous solutions. In addition, the critical micelle concentration (CMC), the surface pressure at CMC (πcmc), the effectiveness of surface tension reduction (pC20), the maximum surface concentration (Γmax) and the minimum area/molecule at the aqueous solution/air interface (Amin) were calculated. Moreover, the biodegradability for these nonionic surfactants has been investigated. Furthermore, the antimicrobial evaluation has been evaluated with some surfactants that have demonstrated a potent cytotoxicity as antibacterial, antifungal and anticancer. These surfactants have a good water solubility, low toxicity, environmentally friendly environment, high foam, good emulsifier and easy production that will be used them in various fields such as medical drugs, insecticides, detergents, emulsifiers, cosmetics, inks clothing, leather industry and oil recovery.

Key words: design, surface properties, antimicrobial activities

1 INTRODUCTION

Surface-active molecules have attracted wide interest for applications due to unique functional properties such as low toxicity and relative ease of preparation used as emulsifiers, wetting, foams, spreading agents and in several industries including organic chemicals, petroleum, petrochemicals, detergents, cosmetics, pharmaceuticals and biotechnological applications⁴⁻³⁰. The presence of hydrophilic and hydrophobic regions in surfactants, which makes them accumulate at the interfaces between hydrocarbons and water, hence reducing surface tension between the surfaces. Thus promoting the transfer of nutrients through membranes and affecting the various host interactions of the microbial⁴⁻³⁰. The surfactants can be used for environmental clean-up through biodegradation, industrial waste disposal and biological treatment of contaminated soils⁶. Also, the biological activities help them to control diseases as therapeutic agents⁷⁻¹⁰. A resistant adhesive against many pathogens suggests that its usefulness as suitable ingredients to combat the coating of adhesives for medical insertion materials results in a reduction in a large number of hospital infections without the use of synthetic drugs⁹. On the other hand, the heterocyclic compounds have a great deal of attention given their interesting therapeutic, biological and pharmaceutical activities¹⁰⁻¹⁵. Heterocyclic derivatives are distributed and necessary for life, which possesses widespread pharmacological properties such as antipyretic and analgesic activities¹⁰. Also, many of these compounds are widely used in nature and in the regular clinical¹⁵,¹⁶. The use of these compounds to synthesize surface active agents has become very important in various fields because of their dual functions as a better surface and biological properties than traditional surface surfaces¹⁷. Because of low toxicity and rapid biological degradation, they are considered one of the pharmaceutical and cosmetic applications¹⁸.

These notes and our interest in the chemistry of heterocycles¹⁹⁻²⁰ prompted us to synthesize various nonionic surfactants factors that carry pyrazole, thiazole, imidazole, pyridine, thiazine, and pyrimidine nucleus using fatty acids and then followed by addition of number of moles of propylene oxide to the list of active hydrogen atoms to form a new class of surface compounds that have declared surface characteristics. Surface parameters, biodegradability and biological activity of the new surfactants were studied.

*Correspondence to: Refat El-Sayed, Chemistry Department, College of Applied Sciences, Umm Al-Qura University, 21955Makkah, SAUDI ARABIA
E-mail: refat_elsayed@yahoo.com
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2 Experimental

All melting points were obtained on a Gallenkamp melting point device using the open capillary method. Infrared spectra were recorded on Thermo scientific spectra (Nicolet iS50 FTIR). The NMR spectra on a Brocker spectrometer operating at 850 MHz were used to record spectra of $^1$H and $^{13}$C NMR using deuterochloroform (CDCl$_3$) as a solvent. Mass spectra have been run on LCMSMS equipment. All spectral analyses were performed at the Magnetic Resonance Center, Faculty of Science, King Abdulaziz University, Saudi Arabia. CHNS elemental analyzer model EA3000 EURO VECTOR used to perform the elemental analysis. Du Nouy tensiometer (Kruss Type 8451) used for measurements the surface properties at 25°C. The biological activity was surveyed at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt.

2.1 Synthesis

2.1.1 Synthesis of (Z)-2-(amino(substituted)methylene)-3-oxoicosanenitrile (4a,b)

A mixture of 2-stearoyl malononitrile 3(2.32g, 7 mmol) and piperidine or morpholine (0.6 mL, 7 mmol) was heated in ethanol (20 mL) for 3hrs and then cooled. The product has been filtered hard and re-crystallized to give the adducts 4a,b, respectively.

(Z)-2-(Amino (piperidin-1-yl)methylene)-3-oxoicosanenitrile (4a)

As green yellow crystals (ethanol), yield (1.83 g, 79%), m.p.: 145-147°C. IR (γ/cm$^{-1}$): 3321-3201 (NH$_2$), 2914, 2847 (aliphatic CH), 2228 (CN), 1698 (CO); $^1$HNMR (δ, ppm): 0.87 (t, 3H, terminal CH$_3$), 1.25-1.44 (m, 32H, 16CH$_2$ of alkyl chain), 1.61 (m, 6H, 3CH$_3$), 2.43 (m, 4H, 2CH$_2$), 4.64 (s, 2H, NH$_2$); $^{13}$CNMR (δ, ppm): 14.1, 22.7, 24.9, 29.0, 29.25, 29.38, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9, 34.0, 56.9, 65.2, 104.2, 168.7, 179.6. Anal. Calcld. (%) for C$_{32}$H$_{57}$N$_3$O (417.67): C, 74.77; H, 11.34; N, 10.06. Found: C, 74.59; H, 11.15; N, 10.24.

(Z)-2-(Amino (morpholinol)methylene)-3-oxoicosanenitrile (4b)

As pale yellow crystals (ethanol), yield (1.71 g, 74%), m.p.: 151-153°C. IR (γ/cm$^{-1}$): 3311-3227 (NH$_2$), 2917, 2850 (aliphatic CH), 2225 (CN), 1687 (CO); $^1$HNMR (δ, ppm): 0.88 (t, 3H, terminal CH$_3$), 1.25-1.62 (m, 32H, 16CH$_2$ of alkyl chain), 2.90 (m, 6H, 2CH$_2$), 3.23 (m, 4H, CH$_2$OCH$_2$), 6.22 (s, 2H, NH$_2$). Anal. Calcld. (%) for C$_{32}$H$_{57}$N$_3$O (419.64): C, 71.55; H, 10.81; N, 10.01. Found: C, 71.32; H, 10.66; N, 10.17.

2.1.2 Synthesis of 1-(3-amino-5-(substituted)-1H-pyrazol-4-yl)-octadecan-1-one (5a,b)

The equivalent amounts of hydroxylamine hydrochloride (0.48 g, 7 mmol) and enamino-nitrile 4a,b (7 mmol), in each case with anhydrous sodium acetate (0.57 g, 7 mmol) were refluxed in glacial acetic acid (20 mL) for 6 hrs. After cooling, the mixture was poured on cold water and then filtered and re-crystallized to give the products 5a,b, respectively.

1-(3-Amino-5-(piperidin-1-yl)-1H-pyrazol-4-yl)octadecan-1-one (5a)

As pale yellow crystals (1,4-dioxane), yield (2.39 g, 82%), m.p.: 119-121°C. IR (γ/cm$^{-1}$): 3321-3284 (NH and NH$_2$), 2915, 2847 (aliphatic CH), 1698 (CO), 1591 (C = N); $^1$HNMR (δ, ppm): 0.86 (t, 3H, terminal CH$_3$), 1.30-1.34 (m, 32H, 16CH$_2$ of alkyl chain), 1.61 (t, 6H, 3CH$_2$), 2.89 (m, 4H, 2CH$_2$), 8.03 (s, 2H, NH$_2$), 11.11 (s, 1H, NH); $^{13}$CNMR (δ, ppm): 14.1, 22.7, 24.7, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 34.0, 93.3, 154.3, 154.6, 179.6; MS: m/z (%): M$^+$ = 432 (18). Anal. Calcld. (%) for C$_{32}$H$_{57}$N$_3$O (432.69): C, 72.17; H, 11.18; N, 12.95. Found: C, 72.38; H, 11.37; N, 12.76.

1-(3-Amino-5-(morpholinol)-1H-pyrazol-4-yl)octadecan-1-one (5b)

As deep yellow crystals (1,4-dioxane), yield (2.26 g, 77%), m.p.: 126-128°C. IR (γ/cm$^{-1}$): 3332-3237 (NH and NH$_2$), 2917, 2848 (aliphatic CH), 1689 (CO), 1580 (CN); $^1$HNMR (δ, ppm): 0.88 (t, 3H, terminal CH$_3$), 1.25-1.41 (m, 32H, 16CH$_2$ of alkyl chain), 2.99 (m, 4H, 2CH$_2$), 3.42 (m, 4H, CH$_2$OCH$_2$), 8.19 (s, 2H, NH$_2$), 10.88 (s, 1H, NH). Anal. Calcld. (%) for C$_{32}$H$_{57}$N$_3$O$_2$ (434.66): C, 69.08; H, 10.67; N, 12.89. Found: C, 69.25; H, 10.49; N, 12.66.

2.1.3 Synthesis of 4-amino-6-(substituted)-5-stearoylpyrimidin-2(1H)-one (6a,b) and 1-(4-amino-6-(substituted)-2-thioko-1,2-dihydropyrimidin-5-yl)octadecan-1-one (7a,b)

A mixture of enaminonitrile 4a,b (7 mmol), sodium ethoxide (0.16 g sodium in 10 mL ethanol, 7 mmol) and urea (0.42 g, 7 mmol) or thiourea (0.53 g, 7 mmol) was stirred in boiling ethanol (15 mL) for 5 hrs, in each case, then cooled. The solution was neutralized by ice/hydrochloric acid. The solid obtained has been filtered and re-crystallized to give the pyrimidine derivatives (6a,b) and (7a,b), respectively.

4-Amino-6-(piperidin-1-yl)-5-stearoylpyrimidin-2(1H)-one (6a)

As light green crystals (1,4-dioxiane), yield (2.16 g, 74%), m.p.: 160-162°C. IR (γ/cm$^{-1}$): 3355-3291 (NH and NH$_2$), 2914, 2847 (aliphatic CH), 1699, 1681 (CO), 1605 (C = C), 1599 (C = N); $^{13}$CNMR (δ, ppm): 14.10, 22.7, 24.7, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 33.9, 58.5, 75.9, 152.0, 158.7, 167.6, 182.6. Anal. Calcld. (%) for C$_{32}$H$_{57}$N$_3$O$_2$ (460.70): C, 70.39; H, 10.50; N, 12.16. Found: C, 70.57; H, 10.67; N, 12.38.

4-Amino-6-(morpholinol)-5-stearoylpyrimidin-2(1H)-one (6b)

As deep yellow crystals (1,4-dioxiane), yield (1.94 g, 66%), m.p.: 167-169°C. IR (γ/cm$^{-1}$): 3338-3256 (NH and NH$_2$), 2917, 2848 (aliphatic CH), 1696, 1680 (CO), 1595 (CN); $^1$HNMR (δ, ppm): 0.89 (t, 3H, terminal CH$_3$), 1.31-1.65 (m, 32H, 16CH$_2$ of alkyl chain), 3.49 (m, 4H, 2CH$_2$),
3.71 (m, 4H, CH₂OCH₂), 8.11 (s, 2H, NH₂), 11.03 (s, 1H, NH). Anal. Caled. (%) for C₂₈H₄₇N₅O₂ (462.77): C, 72.00; H, 10.21; N, 14.80. Found: C, 72.21; H, 10.38; N, 14.29.

2.4-Diamino-6-(piperidino)-5-stearoyl nicotinonitrile (8b)

As brown crystals (1,4-dioxane), yield (2.41 g, 82%), m.p.: 127-129°C. IR (γ/cm⁻¹): 3385-3227 (NH₂), 2918, 2850 (aliphatic CH), 2220 (CN), 1687 (CO); ¹HNMR (δ, ppm): 0.91 (t, 3H, terminal CH₃), 1.22-1.50 (m, 32H, 16CH₃ of alkyl chain), 3.22 (m, 4H, 2CH₂), 3.46 (m, 4H, CH₂OCH₂), 6.85 (s, 2H, NH₂), 7.88 (s, 2H, NH₂). Anal. Caled. (%) for C₃₀H₅₉N₄O₈ (485.71): C, 69.24; H, 9.75; N, 14.42. Found: C, 69.03; H, 9.58; N, 14.27.

2.1.5 Synthesis of (E)-2-(aminosubstituted)methylene-3-oxoicosanoic acid (9a, b)

A mount of enaminitrile 4a, b (7 mmol), in each case was stirred in sulfuric acid (10 mL) for overnight at room temperature and then poured on ice. The precipitate formed was filtered, dried and re-crystallized to produce the products (9a, b), respectively. (E)-2-(aminosubstituted)methylene-3-oxoicosanoic acid (9a)

As light brown crystals (ethanol), yield (2.11 g, 72%), m.p.: 122-124°C. IR (γ/cm⁻¹): 3422-3197 (OH of COOH and NH), 2917, 2850 (aliphatic CH), 1707, 1683 (CO); ¹HNMR (δ, ppm): 0.90 (t, 3H, terminal CH₃), 1.22-1.49 (m, 32H, 16CH₃ of alkyl chain), 1.60 (m, 4H, 2CH₂), 3.26 (m, 4H, CH₂OCH₂), 8.15 (s, 2H, NH₂) and 10.98 (s, 1H, OH). Anal. Caled. (%) for C₃₀H₅₉N₄O₈ (436.67): C, 71.51; H, 11.08; N, 6.42. Found: C, 71.73; H, 11.26; N, 6.61.

2.1.6 Synthesis of (Z)-1-amino-2-(4,5-dihydro-1H-imidazol-2-yl)-1-(substituted)icos-1-en-3-one (10a, b)

Ethylenediamine (2 mL) was added drop-drop to enaminitrile 4a, b (7 mmol) in ethanol (20 mL) with few drops of carbon disulfide, in each case. The mixture was heated for 8 hrs on a water bath. The mixture was treated with cold water. The obtained solid was filtered and re-crystallized to give products (10a, b), respectively. (Z)-1-amino-2-(4,5-dihydro-1H-imidazol-2-yl)-1-(piperidinyl)-icos-1-en-3-one (10a)

As deep yellow crystals (ethanol), yield (2.00 g, 69%), m.p.: 126-128°C. IR (γ/cm⁻¹): 3379-3201 (NH and NH₂), 2914, 2847 (aliphatic CH), 1698 (CO); ¹HNMR (δ, ppm): 0.88 (t, 3H, terminal CH₃), 1.34-1.61 (m, 32H, 16CH₃ of alkyl chain), 1.64 (m, 6H, 3CH₂), 3.40 (m, 4H, 2CH₂), 7.55 (s, 1H, NH), 9.05 (s, 2H, NH₂). ¹CNMR (δ, ppm): 14.1, 22.7, 24.7, 29.0, 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 31.9, 33.9, 51.5, 62.6, 72.2, 157.1, 167.2, 179.6. Anal. Caled. (%) for C₂₂H₃₅N₄O₇ (640.74): C, 72.99; H, 11.38; N, 12.16. Found: C, 72.83; H, 11.47; N, 12.27.

(Z)-1-amino-2-(4,5-dihydro-1H-imidazol-2-yl)-1-(piperidino)-icos-1-en-3-one (10b)

As brown crystals (ethanol), yield (1.91 g, 65%), m.p.: 131-132°C. IR (γ/cm⁻¹): 3364-3187 (NH and NH₂), 2916, 2848 (aliphatic CH), 1684 (CO); ¹HNMR (δ, ppm): 0.89 (t, 3H, terminal CH₃), 1.25-1.52 (m, 32H, 16CH₃ of alkyl chain), 3.17 (m, 4H, 2CH₂), 3.33 (m, 4H, CH₂OCH₂), 7.48 (s, 1H, NH), 8.74 (s, 2H, NH₂). Anal. Caled. (%) for C₂₂H₃₅N₄O₇ (642.71): C, 70.08; H, 10.89; N, 12.11. Found: C, 70.26; H, 10.77; N, 12.24.

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2.1.7 Synthesis of (Z)-1-amino-2-(benzo[d]oxazol-2-yl)-1- (substituted) icos-1-en-3-one (11a,b) and/or (Z)-1-amino-2-(1H-benzo[d]imidazol-2-yl)-1- (substituted) icos-1-en-3-one (12a,b)

Equal amounts of enamionitrile 4a,b (7 mmol) and o-aminophenol or o-phenylenediamine (7 mmol) were heated in ethanol (20 mL) with a few drops of piperidine for 24 hrs. After cooling, the resulting precipitate was filtered and re-crystallized to give products (11a,12a,b, respectively).

(Z)-1-amino-2-(benzo[d]oxazol-2-yl)-1-(piperidin-1-yl) icos-1-en-3-one (11a)

As pale yellow crystals (ethanol), yield (2.25 g, 77%), m.p.: 126-128°C. IR (γ/cm⁻¹): 3354, 3197 (NH₂), 2916, 2849 (aliphatic CH), 1689 (CO); ¹H NMR (δ, ppm): 0.88 (t, 3H, terminal CH₃), 1.32-1.33 (m, 32H, 16CH₂ of alkyl chain), 1.61 (m, 6H, 3CH₂), 2.33 (m, 4H, 2CH₂), 6.86 (s, 2H, NH₂) and 7.26-7.29 (m, 4H, ArH). Anal. Calcd. (%) for C₃₂H₅₂N₄O: 552.86: C, 70.08; H, 10.77; N, 12.24. Found: C, 72.86; H, 11.55; N, 12.31.

(Z)-1-amino-2-(benzo[d]oxazol-2-yl)-1-(morpholino) icos-1-en-3-one (11b)

As deep yellow crystals (ethanol), yield (2.11 g, 72%), m.p.: 132-134°C. IR (γ/cm⁻¹): 3368, 3204 (NH₂), 2914, 2847 (aliphatic CH), 1698 (CO); ¹H NMR (δ, ppm): 0.86 (t, 3H, terminal CH₃), 1.32-1.39 (m, 32H, 16CH₂ of alkyl chain), 3.12 (m, 4H, 2CH₂), 3.38 (m, 4H, CH₂OCH₂), 6.64 (s, 2H, NH₂). Anal. Calcd. (%) for C₃₁H₅₀N₄O₂: 591.89: C, 71.56; H, 9.60; N, 10.26; S, 5.67. Found: C, 72.99; H, 11.38; N, 12.16. Found: C, 72.86; H, 11.55; N, 12.31.

2.1.8 Synthesis of (Z)-N'-(E)-2-cyano-3-oxo-1-(substituted) icos-1-en-1-yl)-N-phenylcarbamimidothioic acid (13a,b)

An equimolar amount of enamionitrile 4a,b (7 mmol), in each case in DMP (20 mL) containing sodium hydroxide (0.28 g, 7 mmol) and phenyl isothiocyanate (0.94 g, 7 mmol) was stirred for 24 hrs. Then poured on ice/hydrochloric acid. The resulting solid was filtered and re-crystallized to produce compounds (13a,b, respectively).

As yellow crystals (ethanol) yield (2.00 g, 70%), m.p.: 129-131°C. IR (γ/cm⁻¹): 3201 (NH₂), 2914, 2847 (aliphatic CH), 2223 (CN), 1698 (CO); ¹H NMR (δ, ppm): 0.87 (t, 3H, terminal CH₃), 1.25-1.63 (m, 32H, 16CH₂ of alkyl chain), 1.63 (m, 6H, 3CH₂), 1.93 (s, 1H, SH), 2.33 (m, 4H, 2CH₂), 7.08-7.43 (m, 5H, ArH), 7.89 (s, 1H, NH). Anal. Calcd. (%) for C₃₅H₅₃N₅OS (591.86): C, 68.76; H, 8.66; N, 11.79; S, 5.40. Found: C, 68.58; H, 8.58; N, 11.62; S, 5.21.

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2.1.10 Synthesis of 1-(4-imino-3-phenyl-6-(substituted))
-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)octadecan-1-one (15a,b)

Phenyl isothiocyanate (0.94g, 7 mmol) was added to en-
aminonitrile 4a,b (7 mmol) in DMF (20 mL) containing tri-
ethylamine (0.5 mL), in each case and then heated for
8hrs. The mixture was poured into ice/water mixture with
a few drops of acetic acid. The product has been filtered
and recrystallized to give pyrimidine derivatives (15a,b),
respectively.

1-(4-Imino-3-phenyl-6-(piperidin-1-yl)-2-thioxo-
1,2,3,4-tetrahydropyrimidin-5-yl)octadecan-1-one (15a)

As reddish yellow crystals (1,4-dioxane/DMF), m.p. 120-
122°C, yield: (2.27 g, 78%). IR (υ/cm⁻¹): 3314, 3224 (NH),
3058 (CH aromatic), 2917, 2850 (CH aliphatic), 1691 (CO).

1HNR (δ, ppm): 0.83 (t, 3H, terminal CH₃), 1.34-1.55 (m,
32H, 16CH₂ of alkyl chain), 1.63 (m, 6H, CH₂), 2.34 (m,
4H, 2CH₂), 7.25-7.77 (m, 6H, ArH and NH), 10.90 (s, 1H,
NH); MS: m/z (M⁺) = 552 (25). Anal. Calcd. (%):
C₂₅H₂₅N₅O₅ (552.86); C, 71.69; H, 9.48; N, 10.13; S, 5.80.
Found: C, 71.55; H, 9.40; N, 10.22; S, 5.67.

2.1.11 Synthesis of 1-(4-amino-6-(substituted)pyrimidin-
5-yl)octadecan-1-one (16a,b)

Formamide (0.3 g, 7 mmol) was added to enaminonitrile
4a,b (7 mmol) in dimethyl formamide (20 mL) with a few
drops of piperidine, in each case, and then heated for
7 hrs. The mixture was poured upon ice/hydrochloric acid for
complete precipitation. The solid obtained was filtered and
re-crystallized to give compounds (16a,b), respectively.

1-(4-Amino-6-(piperidin-1-yl)pyrimidin-5-yl)octadecan-
1-one (16a)

As pale yellow crystals (1,4-dioxane), m.p.; 107-109°C,
yield (2.07 g, 71%). IR (υ/cm⁻¹): 3331, 3216 (NH), 2916,
2849 (CH aliphatic), 1689 (CO); 1HNR (δ, ppm): 0.87 (t,
3H, terminal CH₃), 1.31-1.34 (m, 32H, 16CH₂ of alkyl
chain), 1.61 (m, 6H, CH₂), 2.34 (m, 4H, 2CH₂), 7.82 (s,
2H, NH), 8.83 (s, 1H, CH = N). Anal. Calcd. (%): C₂₅H₂₅N₅O₅
(444.70); C, 72.92; H, 10.88; N, 12.60. Found: C, 72.83;
H, 10.76; N, 12.43.

2-(4-Amino-6-(morpholin-4-yl)pyrimidin-5-yl)octadecan-
1-one (16b)

As deep yellow crystals (1,4-dioxane), m.p.; 115-117°C,
yield (1.94 g, 66%). IR (υ/cm⁻¹): 3407, 3201 (NH), 2914,
1-(6-Imino-4-(morpholino)-2-thioxo-3,6-dihydro-2H-1,3-thiazin-5-yl)octadecan-1-one (18b)

As orange powder (ethanol), yield (1.65 g, 56%), m.p. 123-125°C. IR (\( \nu/cm^{-1} \)): 3365, 3194 (2 NH), 2917, 2848 (aliphatic CH), 2205 (CN), 1674 (CO); \(^1\)HNMR (\( \delta, ppm \)): 0.89 (t, 3H, terminal CH\(_3\)), 1.21-1.44 (m, 32H, 16 CH\(_2\) of alkyl chain), 3.13 (m, 4H, 2CH\(_2\)), 3.15 (m, 4H, 2CH\(_2\)), 3.70 (s, 1H, NH), 10.87 (s, 1H, NH). Anal. Calcd. (\%) for C\(_{35}\)H\(_{52}\)N\(_4\)O\(_2\)S\(_2\) (544.81): C, 74.68; H, 9.22; N, 10.25. Found: C, 74.87; H, 9.40; N, 10.41.

2.1.14 Synthesis of 1-(6-(substituted)-2,4-dithioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)octadecan-1-one (19a,b)

An equal amount of carbon disulfide (0.53 g, 7 mmol) and enaminonitrile 4a,b (7 mmol) in dry pyridine (25 mL), in each case was heated under reflux for 2 hrs. The reaction mixture was cooled, then poured onto ice/water with neutralized with dilute HCl. The solid product has been filtered and re-crystallized to give pyrimidine derivatives (19a,b), respectively.

1-(6-(Piperidin-1-yl)-2,4-dithioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)octadecan-1-one (19a)

As pale yellow crystals (ethanol), yield (2.36 g, 81%), m.p.: 147-149°C. IR (\( \nu/cm^{-1} \)): 3204 (NH), 2914, 2847 (aliphatic CH), 1698 (CO). \(^1\)HNMR (\( \delta, ppm \)): 0.87 (t, 3H, terminal CH\(_3\)), 1.33-1.36 (m, 32H, 16 CH\(_2\) of alkyl chain), 1.61 (m, 6H, 3CH\(_3\)), 2.33 (m, 4H, 2CH\(_2\)), 8.03 (s, 1H, NH), 11.33 (s, 1H, NH). Anal. Calcd. (\%) for C\(_{26}\)H\(_{45}\)N\(_3\)O\(_2\)S\(_2\) (546.79): C, 62.99; H, 9.15; N, 8.48; S, 12.94. Found: C, 62.86; H, 9.27; N, 8.33; S, 12.77.

2.1.15 Synthesis of 4-amino-2-phenyl-6-(substituted)-5-stearoylnicotinonitrile (20a,b)

A solution of enaminonitrile 4a,b (7 mmol) in DMF (20 mL) with piperidine (4 drops) and benzyldine malononitrile (1.08 g, 7 mmol) was heated for 7 hrs, and then left to cool. The reaction mixture was neutralized by ice/water, filtered and re-crystallized to yield pyridine derivatives (20a,b), respectively.

4-Amino-2-phenyl-6-(piperidin-1-yl)-5-stearoylnicotinonitrile (20a)

As reddish yellow crystals (ethanol), yield (1.93 g, 66%), m.p.: 107-109°C. IR (\( \nu/cm^{-1} \)): 3337, 3194 (NH\(_2\)), 2916, 2848 (aliphatic CH), 2216 (CN), 1700 (CO). \(^1\)HNMR (\( \delta, ppm \)): 0.87 (t, 3H, terminal CH\(_3\)), 1.24-1.59 (m, 32H, 16 CH\(_2\) of alkyl chain), 1.60 (m, 6H, 3CH\(_2\)), 2.28 (m, 4H, 2CH\(_2\)), 3.66 (s, 2H, NH\(_2\)), 7.26-7.48 (m, 5H, ArH); MS: m/z (\%) (M\(^+\) = 544.35). Anal. Calcd. (\%) for C\(_{35}\)H\(_{52}\)N\(_4\)O\(_2\)S\(_2\) (546.79): C, 74.68; H, 9.22; N, 10.25. Found: C, 74.87; H, 9.40; N, 10.41.
protons besides the other signals of the compound.

**Compound (31a):** IR (v/cm⁻¹): Broad band at 3408 for (OH), 2925, 2851 (CH aliphatic), 1695 (CO), 1107, 912 (C-O-C) ether of poly propoxy chain; ΗNMR (δ, ppm): Multiple signals in region (3.10–3.79 ppm) for the propoxy protons besides the other signals of the compound.

**Compound (33a):** IR (v/cm⁻¹): Broad band at 3399 for (OH), 2917, 2849 (CH aliphatic), 1666 (CO), 1106, 909 (C-O-C) ether of poly propoxy chain.

**Compound (35a):** IR (v/cm⁻¹): Broad band at 3420 for (OH), 2929, 2854 (CH aliphatic), 1712 (CO), 1129, 905 (C-O-C) ether of poly propoxy chain. Evaluation of the surface properties

2.2.1 Surface and interfacial tension

Surface and interfacial tension characteristics for a solution of the surfactant (10 mmol) were measured using a Kruss du Nouy tensiometer, Type K2 (Kruss GmbH, Hamburg, Germany) at 25°C and the light paraffin oil was used for interfacial tension²⁵.

2.2.2 Cloud point (C.P.)

A cloud point was recorded by heating of the surfactant solution (10 mmol) in deionized water until it became turbid²⁶.

2.2.3 Wetting time

Wetting time was measured in seconds using a solution of the surfactant (10 mmol) and cotton skein (1 g) at 25°C²⁷.

2.2.4 Foaming properties²⁸,²⁹

Place a certain amount of surfactant (10 mmol) in a glass cylinder (100 mL) and circulate for 10 seconds at 25°C, then foam height was measured. Also, the stability of foam was calculated using this expression:

\[
\text{Foam stability} (%) = \frac{(\text{Foam volume after 5 min/Foam volume after 0 min}) \times 100}{100}
\]  

2.2.5 Emulsion stability

The emulsion stability was determined by calculating the time taken to separate the aqueous layer of a mixture of the surfactant (10 mL, 20 mol) and light paraffin oil (6 mL)³⁰.

**Surface parameters for some of the prepared compounds:**

Critical Micelle Concentration (CMC)

CMC of the surfactant was detected using surface tension method of fresh surfactants solutions at different concentrations (0.1 to 0.000005 mol/L). The surface tension values were plotted against the corresponding concentrations²¹.

Efficiency (pC_m)

The efficiency (pC_m) at 25°C has been determined as a negative logarithm of surfactant concentration in the bulk phase required to produce a 20 dyne/cm reduction in the surface tension of the solvent (water)²².

Effectiveness (π_m)

The surface pressure value (effectiveness) of the tested compounds was calculated from the following expression:

\[
\pi_m = \gamma_0 - \gamma_m
\]  

Where γ_m is the surface tension at CMC and γ_0 is the surface tension measured by the pure water at the appropriate temperature²³.

Maximum surface excess concentration (Γ_m)

The maximum surface excess Γ_m was obtained from the relationship:

\[
\Gamma_m = \frac{(\delta \gamma/\delta \log C)}{2.303RT}
\]  

Where (δγ/δ log C) is the slope of the c vs. - Log C plot, T is absolute temperature, R = 8.314 J mol⁻¹ K⁻¹⁴⁰. Minimum surface area per molecule (A_m)

The average area occupied by each adsorbent molecule is given on the interface according to this relationship³¹:

\[
A_m = \frac{10^{19} \Gamma_m}{N}
\]  

Where N is Avogadro's number (6.023 × 10²³) and Γ_m is the maximum surface excess.

2.3 Biodegradability

The biodegradability was carried out by the Die-away test in the River Nile water of the surfactant using a surface tension method³⁴. From the surface tension measurements, the percentage of biodegradation (D%) was calculated as follows:

\[
D = \frac{(\gamma_t - \gamma_0) / (\gamma_0 - \gamma_0) \times 100}{100}
\]  

Where γ₀ = surface tension at zero time, γₜ = surface tension at time t, γ₀ = surface tension of blank experiment at time t (without samples)

2.4 Antimicrobial activity

2.4.1 Antibacterial and antifungal

The new compounds were tested in the laboratory against certain Gram-positive bacteria such as *Staphylococcus aureus* (RCMB010010), *Bacillus subtilis* (NRRL B-543) and Gram-negative bacteria such as *Salmonella typhimurium* (ATCC 14028), *Escherichia coli* (ATCC 25955) and fungi such as *Candida albicans* (ATCC® CRM 10231™), *Aspergillus flavus* (RCMB 002002) using a well diffusion method³⁵.

2.4.2 Anticancer activity

Some of the synthesized compounds were evaluated at different concentrations (3.9, 7.8, 15.6, 31.25, 62.5, 125, 250 and 500 µg mL⁻¹) of their inhibitory activity for the growth of human cancer cells against two cell lines: Hepatocellular carcinoma (HePG2) and colon carcinoma (HCT-116). Cell growth measurements were identified as useful as described in method²⁶,²⁷ and doxorubicin drug was used as a standard reference.
3 RESULTS AND DISCUSSION

3.1 Chemistry

Heterocyclic derivatives combinations with active surface properties and potential pharmaceutical activity were synthesized using fatty acid (1). Where, the heating of 1 with thionyl chloride gave stearoyl chloride 2, which was coupled smoothly with the malononitrile by electrophilic substitution reaction to afford 2-stearoylmalononitrile (3). Treatment of 3 with piperidine or morpholine produced enaminonitrile derivatives 4a,b as a key starting point (Scheme 1). The presence of urea or thiourea with enaminonitrile was added, followed by intramolecular cyclization with the reaction, an initial addition of hydrogen to cyano group and/or of carbon disulfide is furnished the imidazole derivatives (Scheme 1).

Aminonitrile derivatives and their useful role as synthetic intermediates are suitable for building new compounds in one or two easy reaction steps due to possesions a multifunctional unit property. Thus, heating of urea or thiourea with 4a,b were heated with hydroxylamine hydrochloride in glacial acetic acid, in each case and gave the pyrazole derivatives 5a,b.

The presence of cyano and amino groups in the enaminonitrile derivatives that make them highly reactive and widely used as reactants or reaction intermediates, which are conveniently located to enable interactions with active reagents to form a variety of heterocyclic moieties. Thus, compounds 4a,b were heated with hydroxylamine hydrochloride in glacial acetic acid, in each case and gave the pyrazole derivatives 5a,b.

Aminonitrile derivatives and their useful role as synthetic intermediates are suitable for building new compounds in one or two easy reaction steps due to possessions a multifunctional unit property. Thus, heating of urea or thiourea with 4a,b were heated with hydroxylamine hydrochloride in glacial acetic acid, in each case and gave the pyrazole derivatives 5a,b.

Therefore, we investigated the reaction of phenyl isothiocyanate with enaminonitrile derivatives in alkaline medium at a different condition. Thus, phenyl isothiocyanate is stirred with enaminonitrile 4a,b in dimethylformamide containing sodium hydroxide at room temperature producing a nonisolable intermediate (A), which acidified with dil. HCl and gave products 13a,b. Furthermore, heating of the compound 13a,b with chloroacetonitrile in boiling dimethylformamide with a few drops of triethylamine was afforded thiazole derivative 14a,b through the corresponding acyclic intermediate (B) (Scheme 3).

A large variety of reactants carrying (N=C=S) unit is subject to cyclization to interact with different compounds to provide different heterocyclic compounds. Therefore, we have extended our synthetic program to synthesize heterocyclic ring systems using phenyl isothiocyanate. The reaction of enaminonitrile 4a,b with phenyl isothiocyanate in boiling DMF with triethylamine, gave pyrimidine the derivatives 15a,b, respectively, through the intermediate (C). Also, the heating of the enaminonitrile 4a,b with formamide in dimethylformamide with a few drops of piperidine resulted in the formation of pyrimidine derivatives 16a,b. The efficiency of o-aminonitriles toward formic acid is great interest because it is converted by acid or base to the corresponding pyrimidine derivatives. Thus, treatment of enaminonitrile 4a,b with formic acid in ethanol gave the nonisolable intermediate D, which was oxidized by treatment with alkaline hydrogen peroxide to afford pyrimidine derivatives 17a,b. In this reaction, the initial hydration of the nitrile group to the carboxamide was carried out, and then cyclization is carried in alkaline medium.

Scheme 1 Synthesis of the key start compounds (4a,b).
1) SOCl₂, 2) CH₂(CN)₂, 3) Piperidine or morpholine.

Scheme 2 Reactions of the key start compounds (4a,b).
i) NH₂OH/HCl, ii) NH₂CONH₂ or NH₂CSNH₂, iii) CH₂(CN)₂, iv) H₂SO₄, v) NH₂(CH₂)₅NH₂, vi) NH₂CH₂OH(OH) or NH₂CH₂NH₂.
The behavior of enaminonitrile towards carbon disulfide has been studied under different reaction conditions to establish synthetic approaches to more nitrogen heterocyclic derivatives. Thus, stirring of enaminonitrile \(4a, b\) with carbon disulfide in pyridine at room temperature gave the thiazine derivatives \(18a, b\), respectively, by the intermediate (E) (Scheme 4). Furthermore, the heating of \(4a, b\) with the carbon disulfide in pyridine gave the pyrimidine derivatives \(19a, b\). Finally, compounds \(20a, b\) can be obtained by another reaction via the reaction of \(4a, b\) with benzylidene malononitrile in dimethylformamide containing a catalytic amount of piperidine. Newly synthesized compounds were established on their basic analyzes and spectral data (see experimental part).

### 3.2 Preparation of surface-active agents

Nonionic surfactants are amphiphilic chemicals that enhance desorption and bioavailability by increasing the solubility due to their properties: efficiency, economy, ease of handling and formulating, which are used in different applications\(^{40, 41}\). Thus, our aim was to synthesize of surface-active agents containing heterocyclic moiety. Therefore, adding 7 moles of propylene oxide to the prepared compounds (4-20)\(a, b\) in presence of KOH gave nonionic products (21-37)\(a, b\) (Schemes 5 and 6). The compounds that were prepared were based on IR and \(^1\)HNMR spectra (Experimental part). The reaction conditions are summarized in Table 1.

### 3.3 Evaluation of the surface activity

In order to verify the industrial viability of this compounds-based on nonionic surfactants as an alternative to oil or other commercial surfactants. Surface properties and other parameters were assessed and presented in Tables 2 and 3.

#### 3.3.1 Surface and Interfacial tension

Surfactant molecules containing hydrophilic and hydrophobic parts. The hydrophilic part is directed to the water phase and the hydrophobic part is located at the air–water interface. It was found that adsorption of surfactant molecules in the air–water interface decreases the surface tension of the solution. This means that these products have the ability to reduce the surface tension. In comparing, structural surfactants indicated that morpholine derivatives are more effective in reducing the surface tension than piperidine derivatives. Where the surfactants \(35a, b\) showed maximum ability than other the related structure, while compounds \(33a, 36a\) have a low aptitude to reduce the surface tension of aqueous system in the series of amphiphile. Also, pyrimidine derivatives \(32a, b\) revealed...
higher effective than other pyrimidine derivatives. In addition, pyridine derivatives \(25a, b\) revealed higher effective than pyridine derivatives \(27a, b\). Moreover, the surfactants \(22a, b\) and \(29a, b\) showed the same reduction in surface tensions as results in Table 2. On the other hand, the results showed that these compounds have lower interfacial tension values.

3.3.2 Cloud point

Cloud point is an important property for the performance of surfactants and a characteristic observation of the surfactant molecules is that they exhibit a reverse solubility versus temperature behavior in water; therefore, their solutions tend to become evidently muddy at a well-defined temperature, where the surfactant solution phase separates into two phases. The values of the cloud points in Table 2, revealed that the surfactant molecules \(22b, 25b, 30b, 36b\) showed high cloud points, which mean good performance of these compounds in hot water, and reflect the fact that it can use over a wide range of temperatures, which is useful in judging the storage stability of products.

3.3.3 Wetting ability

The ability of wetting property is the most standard for selecting surfactant molecules for use in industrial applications such as the use of textile processing, where the ability of wetting for surfactant molecules may accelerate the diffusion or penetration of alkali chemicals and dyes into the fibers and improve detergency or dyeing effects. The results in Table 2 showed that these molecules have the ability to wet fabric substrates and are more efficient as a wetting agent. Among the studied groups, the surfactant molecules \(22b, 24b, 31b, 37b\) showed the most efficient wetting agents and exhibited shorter drowning time.

3.3.4 Emulsion stability

One of the most important properties of surfactant molecules is emulsion stability for use in a large number of applications such as paints, foam agents, cosmetics and pharmaceutical industries. In fabric processing operations as dyeing and textile scouring, the surfactant’s ability to emulsify oil impurities is critical. Therefore, the surfactants should be added to the dye bath to remove oil impurities from the fibers. The emulsion strength of the surfactant molecule has been detected by dispersion the surfactant from the bulk solution to the interface between oil and water and the physical properties of the adsorbed layers formed from surfactant molecules around the inner phase drop. The results in Table 2 showed that the tested compounds had a low emulsification tendency and therefore their safe applicability in various applications. Among our
products compounds 21b, 24b, 27b, 30b, 32b, 36b showed the shorting time to form emulsion layer.

3.3.5 Foaming Properties
Surfactant molecules are very useful in various applications, requiring a small or large amount of foam as in the dying process; however, foams can be undesirable; they are created by passing gas in liquid during the movement of machines. In addition, in washing the hair, the foam of the shampoo not only surrounds the grease but also imparts to the company’s sense and fulfillment; it will feel unpleasant if the foam to disappear immediately. In our study, the foam performance of the surfactant molecules of the initial foam (after 0 min observation) was performed and the foam stability (after 5 minutes). The results in Table 2 showed that the foam heights of our products ranged from 35 and 46 mm, which mean that these products showed foam properties.

3.3.6 Evaluation of some surface parameters
The critical micelle concentration (CMC), effectiveness (πcmc), efficiency (pC20), maximum surface excess (Γma.), and minimum surface area (Amin) were investigated of some of the synthesized compounds (21,22,24-29,32,34,36,37) a,b and summarized in Table 3.

3.3.6.1 Critical micelle concentration (CMC)
The efficiency of surfactant molecules can be determined by the CMC property, which reveals the required amount of surfactant molecule to reach the maximum reduction of surface tension. Where the surfactant molecule has a low value of CMC that enjoys excellent emulsion, solubility and detergency properties. When surfactant concentration is increased, surface tension decreases steadily and at critical concentrations, there is no significant reduction in surface tension. This demonstrates the realization of saturation in the surface adsorbed layer and starting the forming of micelle in the bulk. Of the results in Table 3, it is obvious for testing surfactants that a sharp reduction in surface tension was observed with increased concentration. The increase in the value of CMC obtained can be attributed to an increase in the solubility of the surfactant molecules i.e., the presence of an oxygen or nitrogen atom in a chain of hydrophobic as polar atoms lead to an increase in the CMC.

3.3.6.2 Effectiveness (πcmc)
An important factor in determining the surface properties is the effectiveness of adsorption. In addition, the difference between the surface tension of distilled water and the CMC values were used to determine the effectiveness (πcmc) of the amphiphilic molecules. The maximum reduction in surface tension due to the dissociation of surfactant molecule has been indicated by the effectiveness πcmc.
which becomes a measure of the effectiveness of the am-
phiphile to reduce the surface tension of water. In general,
the results in Table 3 show that the tested compounds
have the potential to reduce the surface tension in the
aqueous system. Moreover, the effectiveness values ranged
from 29.2 to 43.4 dyne/cm.

3.3.6.3 Efficiency \( \text{pC}_{20} \)

The concentration of surfactant molecule required to
give 20 mN/m reduction in surface tension is known as the
efficiency of surfactant adsorption \( \text{pC}_{20} \). In comparing the
adsorption efficiency of air/water interface of the surfac-
tant molecule, the adsorption efficiency values are very im-

| Sample | Temperature °C | Propoxylated products | Yield % | Solvent of crystallization | Color | Shape |
|--------|----------------|------------------------|---------|---------------------------|-------|-------|
| 4a     | 140-150        | 21a                    | 79      | Benzene                   | Deep brown | Solid |
| 4b     | 150-160        | 21b                    | 77      | Benzene                   | Light brown | Solid |
| 5a     | 115-125        | 22a                    | 82      | Ethanol                   | Pale yellow | Semi-solid |
| 5b     | 120-130        | 22b                    | 79      | Ethanol                   | Brown      | Semi-solid |
| 6a     | 150-160        | 23a                    | 84      | Methanol                  | Pale yellow | Solid |
| 6b     | 150-160        | 23b                    | 82      | Methanol                  | Orange     | Solid |
| 7a     | 155-165        | 24a                    | 80      | Ethanol                   | Deep yellow | Solid |
| 7b     | 160-170        | 24b                    | 78      | Ethanol                   | Yellow     | Solid |
| 8a     | 115-125        | 25a                    | 83      | Ethanol                   | Deep orange | Semi-solid |
| 8b     | 120-130        | 25b                    | 80      | Ethanol                   | Light brown | Semi-solid |
| 9a     | 110-120        | 26a                    | 76      | Ethanol                   | White yellow | Oil |
| 9b     | 120-130        | 26b                    | 76      | Ethanol                   | Orange     | Oil |
| 10a    | 120-130        | 27a                    | 77      | Benzene                   | Yellow     | Semi-solid |
| 10b    | 125-135        | 27b                    | 75      | Benzene                   | Pale yellow | Semi-solid |
| 11a    | 120-130        | 28b                    | 80      | Ethanol                   | Reddish brown | Semi-solid |
| 11b    | 130-140        | 28b                    | 79      | Ethanol                   | Brown      | Semi-solid |
| 12a    | 110-120        | 29a                    | 78      | Ethanol                   | Brown      | Oil |
| 12b    | 120-130        | 29b                    | 77      | Ethanol                   | Brown      | Oil |
| 13a    | 125-135        | 30a                    | 81      | Ethanol                   | Light brown | Oil |
| 13b    | 130-140        | 30b                    | 79      | Ethanol                   | Brown      | Oil |
| 14a    | 105-115        | 31a                    | 82      | Methanol                  | Pale yellow | Oil |
| 14b    | 115-125        | 31b                    | 80      | Methanol                  | Deep yellow | Oil |
| 15a    | 115-125        | 32a                    | 78      | Ethanol                   | Brown      | Semi-solid |
| 15b    | 125-130        | 32b                    | 77      | Ethanol                   | Brown      | Semi-solid |
| 16a    | 105-115        | 33a                    | 82      | Ethanol                   | Light brown | Oil |
| 16b    | 110-120        | 33b                    | 80      | Ethanol                   | Deep brown | Oil |
| 17a    | 100-110        | 34a                    | 83      | Ethanol                   | Deep yellow | Oil |
| 17b    | 110-120        | 34b                    | 80      | Ethanol                   | Brown      | Oil |
| 18a    | 105-115        | 35a                    | 77      | Benzene                   | Yellow     | Semi-solid |
| 18b    | 120-130        | 35b                    | 75      | Benzene                   | Pale yellow | Semi-solid |
| 19a    | 140-150        | 36a                    | 80      | Ethanol                   | Deep yellow | Solid |
| 19b    | 150-160        | 36b                    | 79      | Ethanol                   | Brown      | Solid |
| 20a    | 100-110        | 37a                    | 80      | Ethanol                   | Deep brown | Oil |
| 20b    | 110-120        | 37b                    | 79      | Ethanol                   | Deep brown | Oil |
Synthesis of Functional Surfactants

Table 2  Surface properties of the synthesized compounds (21-37) a,b.

| Sample | S. T (dyne/cm) | I. T (dyne/cm) | C.P °C | Wetting (sec) | Emulsion Stability (min) | Foam height 0 min (mm) | Foam height 5 min (mm) | Foaming stability (%) |
|--------|----------------|----------------|--------|---------------|---------------------------|------------------------|------------------------|----------------------|
| 21a    | 35             | 9.1            | 68     | 86            | 26                        | 47                     | 36                     | 76.59                |
| 21b    | 35             | 8.7            | 76     | 79            | 18                        | 50                     | 41                     | 82.00                |
| 22a    | 39             | 11.3           | 73     | 92            | 52                        | 48                     | 37                     | 77.08                |
| 22b    | 38             | 10.6           | 81     | 74            | 46                        | 70                     | 55                     | 78.57                |
| 23a    | 38             | 13.8           | 66     | 99            | 33                        | 55                     | 41                     | 74.54                |
| 23b    | 37             | 11.3           | 76     | 93            | 27                        | 73                     | 54                     | 73.97                |
| 24a    | 39             | 12.8           | 71     | 84            | 29                        | 31                     | 22                     | 70.96                |
| 24b    | 37             | 12.0           | 79     | 75            | 18                        | 46                     | 35                     | 76.08                |
| 25a    | 40             | 14.6           | 76     | 98            | 35                        | 42                     | 34                     | 80.95                |
| 25b    | 38             | 10.8           | 81     | 86            | 26                        | 50                     | 43                     | 86.00                |
| 26a    | 37             | 11.3           | 66     | 93            | 31                        | 28                     | 19                     | 67.85                |
| 26b    | 34             | 10.7           | 71     | 85            | 20                        | 48                     | 37                     | 77.08                |
| 27a    | 39             | 13.2           | 68     | 98            | 28                        | 37                     | 21                     | 56.75                |
| 27b    | 36             | 9.8            | 75     | 92            | 18                        | 49                     | 36                     | 73.46                |
| 28a    | 37             | 14.2           | 70     | 95            | 35                        | 28                     | 22                     | 78.57                |
| 28b    | 34             | 13.0           | 76     | 89            | 28                        | 27                     | 19                     | 70.37                |
| 29a    | 39             | 11.7           | 68     | 97            | 37                        | 37                     | 25                     | 67.56                |
| 29b    | 36             | 9.8            | 75     | 93            | 25                        | 52                     | 38                     | 73.07                |
| 30a    | 38             | 13.6           | 74     | 88            | 25                        | 49                     | 38                     | 77.55                |
| 30b    | 37             | 13.2           | 80     | 81            | 17                        | 78                     | 66                     | 84.61                |
| 31a    | 37             | 11.6           | 62     | 78            | 35                        | 36                     | 25                     | 69.44                |
| 31b    | 35             | 10.5           | 70     | 74            | 29                        | 56                     | 41                     | 73.21                |
| 32a    | 37             | 10.4           | 65     | 89            | 28                        | 39                     | 26                     | 66.66                |
| 32b    | 34             | 8.5            | 74     | 84            | 18                        | 51                     | 39                     | 76.47                |
| 33a    | 41             | 14.4           | 72     | 91            | 41                        | 25                     | 17                     | 68.00                |
| 33b    | 39             | 14.0           | 77     | 85            | 32                        | 38                     | 31                     | 81.57                |
| 34a    | 39             | 11.7           | 69     | 99            | 25                        | 10                     | 8                      | 80.00                |
| 34b    | 36             | 9.5            | 74     | 89            | 22                        | 37                     | 24                     | 64.86                |
| 35a    | 31             | 12.4           | 65     | 90            | 41                        | 43                     | 33                     | 76.74                |
| 35b    | 30             | 11.8           | 70     | 83            | 38                        | 55                     | 40                     | 72.72                |
| 36a    | 42             | 11.2           | 76     | 87            | 22                        | 51                     | 43                     | 84.31                |
| 36b    | 38             | 9.7            | 80     | 85            | 17                        | 62                     | 51                     | 82.25                |
| 37a    | 39             | 14.7           | 69     | 78            | 44                        | 32                     | 21                     | 65.62                |
| 37b    | 37             | 13.6           | 78     | 72            | 34                        | 51                     | 38                     | 74.51                |

Error of measurements was: Surface Tension (S.T) and Interfacial Tension (IFT) = ±0.1 dynes/cm. Cloud point (C.P) = ±1°C. Wetting time = ± 1 sec. Emulsion = ± 1 min. Foam height = ± 2 mm.

Because of this absorption between water molecules, the surfactant molecule reduces the surface tension. The greater Pc20 value, the more efficient surfactant molecule to reduce the surface tension and the more efficient the adsorbent in the interface. The results in Table 3 show that the tested molecules have a good tendency to their surface activity.
3.3.6.4 Maximum surface excess $\Gamma_{ma}$

The value of maximum surface excess $\Gamma_{ma}$ is very useful to measure the effectiveness of compound adsorption. So the material will reduce surface tension and thus exist excess when or near the surface. Pumping of surfactant molecules into the boundary surfaces between the phases of the formation of the adsorbed layer is one of the most objective applications of surfactants as a vital branch of chemistry in many applications. In addition, when the surface tension is reduced give a clear activity of the compound. Values of $\Gamma_{ma}$ were calculated and listed in Table 3.

3.3.6.5 Minimum surface area $A_{min}$

Based on the minimum surface area of the surfactant molecules in the air/water interface in the surface saturation, it gives some information about the degree of packing and orientation of the surface tension adsorbent molecule. The results in Table 3 showed that all the testing surfactants had lower $A_{min}$ values, which indicated highly packed molecules in the interface. The values of area per molecule showed that these molecules were located in the tail position on the surface.

3.3.7 Biodegradability

The biodegradability of the tested compounds was recorded in Table 4, which showed that these surfactants factors are determined as biodegradable compounds and pass international level (98% after 8 days), which means that the biodegradation of these surfactants significantly reduces the toxicity and safety of human as well as the environment. Where the compounds 22a,b, 33a,b, 34a,b and 36a,b showed above 90% degradation after 7 days than the remaining compounds.

3.3.8 Biological assessment

3.3.8.1 Antibacterial activity

Some testing compounds showed varying inhibitory effects on the growth of bacterial strains. The results in Table 5 indicated that the pyrimidine derivative 36a showed the best biological activity against Bacillus subtilis. While the pyrimidine derivative 24b showed better biological activity against Staphylococcus aureus. On the other hand, the piperidine derivative 30a revealed better...
biological activity against *Escherichia coli* compared with the reference. Moreover, the thiazole derivative 31a showed good activity toward *Salmonella typhimurium*.  

3.3.8.2  Antifungal activity  

The results depicted in Table 5, revealed that some tested compounds exhibit a varying degree of microbial inhibition as antifungal agents. Where, the pyrimidine 23a, pyridine 24b, thiazine 35a, and pyrimidine 36a derivatives exhibited better antifungal potentials than other compounds against *Aspergillus flavus*. In addition, we observed that the pyrimidine derivatives 32b and 36a exhibited broad-spectrum antifungal profile against *Candida albicans*. In conclusion, the nature of substituents and heterocyclic skeleton of molecules have a strong impact on the extent of antibacterial and antifungal activities.
Some of the tested compounds were evaluated for their in vitro cytotoxicity against two cell lines of human cancer: HepG2 and HCT-116 at different concentrations with use the doxorubicin as a reference drug. The viability cells were determined by the colorimetric method. The calculated response parameter was the value of IC_{50}, which corresponds to the concentration required for 50% inhibition of cell viability. The inhibitory concentration fifty (IC_{50}) for the tested compounds of HepG2 and HCT-116 was calculated from Tables 6 and 7, respectively. The results of inhibitory concentration fifty (IC_{50}) data were summarized in Table 8.
and showed that some of the tested compounds revealed significant activity as reference drug. In particular, piperidine derivative 30a, which has shown the best significant against two cell lines of antitumor cancer. Where the compound 30a has less IC_{50} values than other tested compounds against (HePG2) and (HCT-116). These preliminary results of the biological examination of the tested compounds give an idea of the potential importance of these compounds acting against bacteria, fungi, and cancer, which give an encouraging framework in the field that may lead to the discovery of a potent microbial agent.

4 CONCLUSION
New classes of environmentally safe surface active agents bearing heterocyclic nucleus such as piperidine, morpholine, pyrazole, thiazole, imidazole, pyridine and pyrimidine derivatives in different molecular weights have been designed and synthesized from renewable and easily available resources. Propoxylation of these heterocycles was produced nonionic surfactants (21-37) with surface-active properties, which showed good degradation susceptibility within 7-8 days. The newly compounds (21-37) exhibit varying degrees of microbial inhibition such as antibacterial, antifungal and anticancer. Some of these compounds revealed that the most effective cells against human hepatocellular cancer cells (HePG2) and human colon carcinoma (HCT-116). Therefore, these surfactants have low toxicity to human and environment because of their solubility and good biodegradability. Moreover, they can be used in different fields as cosmetics, dyes, emulsifiers, drugs, pesticides and many other industries.

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REFERENCES
1. Vijayakumar, S.; Saravanan, V. Biosurfactants-types, sources and applications. Res. J. Microbiol. 10, 181-
1) Magdalena, P.; Gražyna, A.P.; Zofia, P.S.; Swaranjit, S.C. Environmental applications of biosurfactants: recent advances. *Int. J. Mol. Sci.* 12, 633-654 (2011).

2) Rita de Cássia, F.S.S.; Darne, G.A.; Raquel, D.R.; Juliana, M.L.; Valdemir, A.S.; Leonie, A.S. Applications of biosurfactants in the petroleum industry and the remediation of oil spills. *Int. J. Mol. Sci.* 15, 12523-12542 (2014).

3) Banat, I.M.; Franzetti, A.; Gandolfi, I.; Bestetti, G.; Martinotti, M.G. Microbial biosurfactants production, applications and future potential. *Appl. Microbiol. Biotechnol.* 87, 427-444 (2010).

4) Volkering, F.; Breure, A.M.; Rulkens, W.H. Microbiological aspects of surfactant use for biological soil remediation. *Biodegradation* 8, 401-417 (1998).

5) Olivera, N.L.; Commendatore, M.G.; Delgado, O.; Esteves, J.L. Microbial characterization and hydrocarbon biodegradation potential of natural bilge waste microflora. *J. Ind. Microbiol. Biotechnol.* 30, 542-548 (2003).

6) Mirela, E.; Ana, M.T.; Madalin, I.E. Mitoxantrone-surfactant interactions: A physic-chemical overview. *Molecules* 21, 1356-1372 (2016).

7) Raquel, P.; Maria, R.A.; Francisco, J.P.; Mar, F.; Juan, P.; Carolina, S.; Ricardo, S.; Laura, R.; Julio, S.R. Anticancer and antiangiogenic activity of surfactant-free nanoparticles based on self-assembled polymeric derivatives of vitamin E: Structure-activity relationship. *Biomacromolecules* 16, 1566-1581 (2015).

8) Bhairav, P.; Harjot, P.K.; Sukhvir, K. Potential biomedical and pharmaceutical applications of microbial surfactants. *World J. Pharm. Sci.* 4, 1557-1575 (2015).

9) Mostafa, M.G.; Mansour, S.A. Anti-breast cancer activity of some novel quinoline derivatives. *Acta Pharm.* 65, 271-283 (2015).

10) Elham, S.D.; Azza, M.A.; Favzy, A.A.; Oqba, N.A. Synthesis and antimicrobial evaluation of some novel thiazole, pyridone, pyrazole, chromene, hydrazone derivatives bearing a biologically active sulfonamide moiety. *Int. J. Mol. Sci.* 15, 1237-1254 (2014).

11) Alafeefy, A.M.; Isik, S.; Abdel-Aziz, H.A.; Ashour, A.E.; Vullo, D.; Al-Jaber, N.A.; Supuran, C.T. Carbonic anhydrase inhibitors: Benzensulfonylamides incorporating cyano-acrylamide moieties are low nanomolar/sub-nanomolar inhibitors of the tumor-associated isozymes IX and XII. *Bioorg. Med. Chem.* 21, 1396-1403 (2013).

12) Azab, M.E.; Youssef, M.M.; El-Bordany, E.A. Synthesis and antibacterial evaluation of novel heterocyclic compounds containing a sulfonamido moiety. *Molecules* 18, 832-844 (2013).

13) Asmaa, S.S.; Naema, A.M.; Anhar, A.; Mona, A.M.; Doaa, M.E. Synthesis, reactions and antimicrobial activity of some new 3-substituted indole derivatives. *Int. J. Org. Chem.* 5, 81-99 (2015).

14) Sawsan, A.F. Synthesis, characterization and anti-breast cancer activity of some new pyrazole, thiazole, chromene and pyridine derivatives. *Int. J. Adv. Res.* 2, 442-453 (2014).

15) Samir, B.; Abd El-Gaber, T.; Ahmed, A.F. Regioselective synthesis of some new pyrazolo[1,5-a]pyrimidines, pyrazolo[1,5-a]quinazoline and pyrimido[4,5,3,4-pyrazolo[1,5-a] pyrimidines containing thiazone moiety. *J. Heterocyclic Chem.* 52, 1792-1799 (2015).

16) El-Sayed, A.E.; Attia, I.M.; Mohamed, A.M.A.; Ahmed, M.T. Synthesis and physico-chemical properties of sodium 3-oxo-2-(3-(4-sulphonatophenyl)triaz-2-yl)octadecanoate anionic surfactant. *J. Surfact. Detery.* 19, 573-582 (2016).

17) El-Sayed, A.E.; Attia, I.M.; Mohamed, A.M.A.; Ahmed, M.T. Synthesis and physico-chemical properties of sodium 3-oxo-2-(3-(4-sulphonatophenyl)triaz-2-yl)octadecanoate anionic surfactant. *J. Surfact. Detery.* 19, 573-582 (2016).

18) Poonam, K.; Pawan, K.; Arpna, M.; Neeraj, K.A.; Pawan, K.S. Synthesis of some novel 4-arylidene pyrazoles as potential antimicrobial agents. *Org. Med. Chem. Lett.* 3, 1-7 (2013).

19) El-Sayed, R. Surface pharmaceutical application of pyrazole, isoxazole, pyrimidine and pyridine derivatives. *Afinidad LXX.* 562, 142-148 (2013).

20) El-Sayed, R. Substituted thiazidazole, oxazidazole, triazole and triazinone as antimicrobial and surface activity compounds. *J. Surfact. Detery.* 16, 39-47 (2013).

21) El-Sayed, R.; Khalid, S.K. Propoxylated fatty thiazole, pyrazole, triazole, and pyrrole derivatives with antimicrobial and surface activity. *J. Surfact. Detery.* 18, 661-673 (2015).

22) El-Sayed, R. Synthesis and heteroanannulation of pyridine and related heterocyclic systems having surface and biological activities. *J. Oleo Sci.* 64, 761-774 (2015).

23) El-Sayed, R. Synthesis of biodegradable pyrazole, pyran, pyrrole, pyrimidine and chromene derivatives having medical and surface activities. *J. Surfact. Detery.* 19, 1153-1167 (2016).

24) Morgos, J.; Sallay, P.; Farkas, L.; Rusznak, I. A new approach of ethoxylation catalyzed by bridge head nitrogen containing compounds. *J. Am. Oil Chem. Soc.* 60, 1905-1907 (1983).

25) Findlay, A. *Practical physical chemistry.* 6th ed. Longmans, London pp. 1039-1040 (1963).

26) Durham, K. Properties of detergent solutions-amphipathic and adsorption, surface activity and detergency. in *Surface activity and detergency* Vol. 1, MacMillan & Co. Ltd., London, pp. 1-28 (1961).

27) Draves, C.Z.; Clarkso, R. A new method for the evaluation of wetting agents. *J. Am. Dye Stuff Reporter* 20, 201-209 (1931).

28) Ross, J.; Milles, G.D. Apparatus for comparison of foaming properties of soaps and detergents. *Oil Soap* 18, 99-102 (1941).
29) Saito, Y.; Sato, T.; Anazawa, I. Correlation between distribution of oxyethylene chain and physicochemical properties of nonionic surfactants. *Yakuzaigaku* 49, 180-183 (1989).

30) Eter, E.T.; Richard, R.E.; David, A. Biodegradability surfactants derived from cornstarch. *J. Am. Oil Chem. Soc.* 51, 486-494 (1974).

31) Hikota, T.; Meguro, K. Preparation and properties of sodium alkyl β-sulphopropionates. *J. Am. Oil Chem. Soc.* 47, 158-161 (1970).

32) Rosen, M. Relationship of structure to properties in surfactants: II. Efficiency in surface or interfacial tension reduction. *J. Am. Oil Chem. Soc.* 51, 461-465 (1974).

33) Rosen, M.J.; Aronson, S. Standard free energies of adsorption of surfactants at the aqueous solution/air interface from surface tension data in the vicinity of the critical micelle concentration. *Colloids Surf.* 3, 201-208 (1981).

34) Falbe, J. *Surfactants for Consumer* Vol. 4, Springer Verlag, Heidelberg, Germany, pp. 139-141 (1986).

35) Ibrahim, H.S.; Eldehna, W.M.; Abdel-Aziz, H.A.; Elaasser, M.M.; Abdel-Aziz, M.M. Improvement of antibacterial activity of some sulfa drugs through linkage to certain phthalazin-1(2H)-one scaffolds. *Eur. J. Med. Chem.* 85, 480-486 (2014).

36) Mosmann, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* 65, 55-63 (1983).

37) Gomha, S.M.; Riyadh, S.M.; Mahmoud, E.A.; Elaasser, M.M. Synthesis and anticancer activities of thiazoles, 1,3-thiazines and thiazolidine using chitosan-grafted-poly(vinyl-pyridine) as basic catalyst. *Heterocycles* 91, 1227-1243 (2015).

38) Howsaway, H.O.; El-Sayed, R. Synthesis of potential pharmaceutical heterocycles as surface active agents. *J. Surfact. Deterg.* 20, 681-694 (2017).

39) Fadda, A.A.; Khalil, A.M.; Tawfik, E.H. Enaminonitriles in heterocyclic synthesis: synthesis and biological evaluation of novel indeno[2,1-b]thiophene derivatives. *Turk. J. Chem.* 37, 134-148 (2013).

40) Maguire, R.J. Review of the persistence of nonylphenol and nonylphenol ethoxylates in aquatic environments. *Water Qual. Res. J.* 34, 37-78 (1999).

41) Ivanković, T.; Hrenović, J. Surfactants in the environment. *Arh. Hig. Rada. Toksikol.* 61, 95-110 (2010).