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Propoxylated Fatty Thiazole, Pyrazole, Triazole, and Pyrrole Derivatives with Antimicrobial and Surface Activity

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Abstract Lauric acid and propylene oxide were used to modify four biologically active heterocycles (thiazole, pyrazole, triazole, and pyrrole) to synthesize 17 new surfactants. The chemical structures of these surfactants were confirmed using infrared and ^{1}H, and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The surfactants all show good surface activity, low critical micelle concentration (CMC) values, high cloud points, and tight interfacial packing. All showed antimicrobial activity on both bacteria and fungi. In addition, biodegradation testing demonstrated significant breakdown within seven days.

Keywords Synthesis · Heterocycle derivatives · Propoxylation · Antimicrobial properties · Surface activities

Introduction

Fatty acid hydrazides containing an amide group attached to a primary amine group have wide application in pharmaceutical studies [1, 2]. Hydrazides have demonstrated effectiveness against tuberculosis [3]. 1,3,4-Oxadiazoles are biologically active materials used in medical science and agriculture [4]. 1,3,4-Thiadiazoles are reported to have anti-inflammatory, antimicrobial, and anticonvulsant efficacy [5–7]. The triazole nucleus has a reported antitumor effect [8–10]. Finally, the thiadiazole nucleus has demonstrated antibacterial, antiviral, and antioxidant results [11–13].

In view of these applications of fatty acid heterocyclic derivatives as biologically active agents [14], we developed a new synthetic method to modify these derivatives to increase surface activity and, perhaps, antimicrobial potency [15]. This builds on our previous synthetic work on biologically important heterocyclic compounds. Oleochemicals are essential to a variety of industries such as coatings, surfactants, plasticizers, lubricant additives, cosmetics, pharmaceuticals, soaps, detergents, textiles, plastics, and as mild surfactants in cosmetic formulations [16, 17].

In view of the above mentioned facts and in continuation of our work on the syntheses of biologically important heterocyclic compounds [18–21], we investigate an efficient synthesis with the goal of obtaining more potent surface activity and pharmacologically active compounds.

Experimental Section

Materials and Methods

The chemicals, with 98 % purity. used in the synthesis of all compounds were obtained from the Sigma-Aldrich Chemical Company. The solvents used were of spectroscopic grade and used without further purification.

Melting points were determined by the open capillary method using a Gallen Kamp melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide (KBr) discs on a FTIR 8300 Shimadzu spectrophotometer and the results are expressed in wave number (cm^{-1}). ^{1}H, and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AC300 spectrometer (Fällanden, Switzerland) operating at

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300 MHz for ^{1}H and 75 MHz for ^{13}C, using deuterochloroform (CDCl$_3$) as a solvent. Chemical shifts are expressed in δ (ppm) using tetramethylsilane (TMS) as the internal standard. Elemental microanalysis was carried out using a CHNS (carbon, hydrogen, nitrogen, sulfur) elemental analyzer model EA3000 EURO VECTOR instruments. Biological activity was screened at the Microbiology Department, Faculty of Applied Science, Umm Al-Qura University, Saudi Arabia.

Synthesis of Hetrocyclic Compounds (Schemes 1, 2)

Synthesis of Ethyl Dodecanoate (2)

A mixture of lauric acid (**1**) (2 g, 0.01 mol), absolute ethanol (50 mL) and conc. H$_2$SO$_4$ (0.5 ml) was refluxed for 8–10 h in a round bottom flask and then cooled to 5 °C. The solvent was removed by distillation and the reaction mixture washed with 1 % aqueous sodium bicarbonate solution. The reaction mixture was extracted with ethyl acetate and the solid separated was dried over magnesium sulfate, filtered, and collected to obtain compound **2**.

Synthesis of Dodecane Hydrazide (3)

To a solution of **2** (2.28 g, 0.01 mmol) in absolute absolute ethanol (30 mL), hydrazine hydrate (0.64 g, 0.02 mol) was added and the reaction mixture was heated under reflux for 6 h and then left to cool. The solid product was collected by filtration and purified by crystallization form ethanol. White powder, (1.93 g, 85 %), mp. 115–117 °C. IR (ν/cm^{-1}): 3342–3225 (NH, NH$_2$), 2953, 2848 (CH in alkyl chain) and 1676 (C=O). ^{1}H NMR: δ 6.83 (s, 1H, NH), 3.92 (s, 2H, NH$_2$), 0.95 (t, 3H, terminal CH$_3$), 1.40–1.25 (m, 20H, CH$_2$ in alkyl chain). Anal. Calc. for C$_{12}$H$_{26}$N$_2$O (214.35): C, 67.24; H, 12.23; N, 13.07 %. Found: C, 66.98; H, 11.97; N, 12.78 %.

Synthesis of N-Phenyl-5-undecyl-1,3,4-oxadiazol-2-amine (4)

A mixture of hydrazide **3** (2.14 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in dimethylformamide (20 mL) was heated under reflux for 8 h. The reaction was cooled and the solvent evaporated under reduced pressure. The solid product obtained was crystallized from a mixed solvent ethanol and dimethylformamide (10:10). Yellow solid, (1.39 g, 65 %), mp. 96–98 °C. IR (ν/cm^{-1}): 3221 (NH), 3091 (CH aromatic), 2950, 2848 (CH aliphatic) and 1618, 1597 (C=N). ^{1}H NMR: δ 8.00 (s, 2H, NH), 7.38–7.47 (m, 5H, ArH), 1.36–1.26 (m, 20H, CH$_2$ in alkyl chain), 0.89 (t, 3H, terminal CH$_3$). Anal. Calc. for C$_{19}$H$_{29}$N$_3$O (315.45): C, 72.34; H, 9.27; N, 13.32 %. Found: C, 72.61; H, 9.57; N, 13.11 %.

Synthesis of 3-Undecyl-1H-1,2,4-triazole-5(4H)-thione (5)

Equimolar amounts of hydrazide **3** (2.14 g, 0.01 mol) and ammonium thiocyanate (0.76 g, 0.01 mol) in (50 mL)

Scheme 1 Synthesis of oxadiazole **4**, triazole **5**, pyrazole **6**, indole **7**, triazole **9**, thiadiazole **10**, and thiazole **11** derivatives
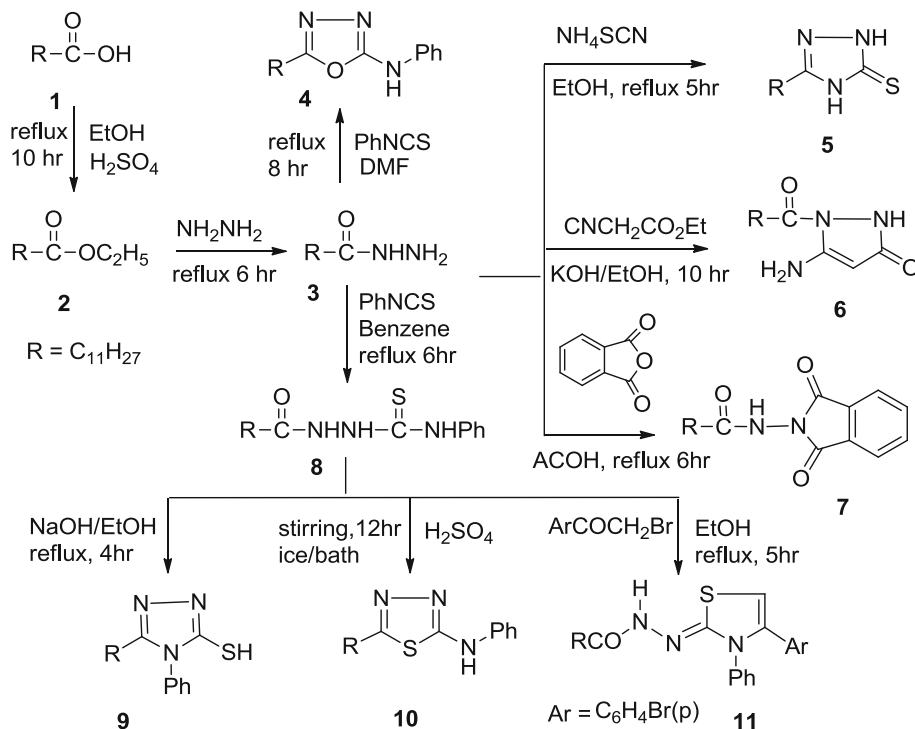
Scheme 2 Synthesis of thiazole **13**, pyrazole **14**, pyrrole **15**, oxadiazine **16**, oxadiazole **17**, triazole **18**, and thiadiazole **19** derivatives

R = C₁₁H₂₇
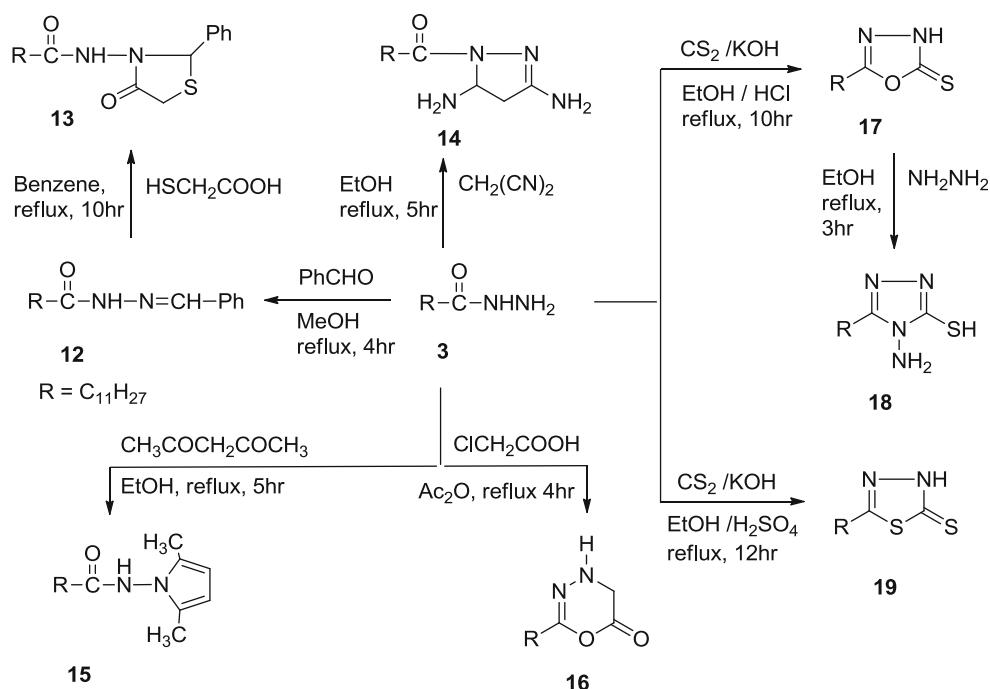
ethanol with (5 mL) hydrocholoric acid was heated under reflux for 5 h. The solid that appeared on cooling was filtered and recrystallized from ethanol. White powder, (1.32 g, 62 %, mp. 97–99 °C. IR (ν/cm⁻¹): 3314–3289 (NH), 2954, 2848 (CH aliphatic) and 1597 (C=N). ¹H NMR: δ 8.40, 12.14 (2 s, 2H, 2NH), 1.23–1.30 (m, 20H, CH₂ in alkyl chain), 0.91 (t, 3H, terminal CH₃). ¹³C NMR: δ 175.63, 153.19, 35.96, 31.32, 29.99, 29.54, 29.24, 29.16, 28.93, 26.84, 25.82, 24.78, 22.57. Anal. Calc. for C₁₃H₂₅N₃S (255.42): C, 61.13; H, 9.87; N, 16.45; S, 12.55 %. Found: C, 60.90; H, 9.68; N, 16.12; S, 12.19 %.

Synthesis of 5-Amino-1-dodecanoyl-1H-pyrazol-3(2H)-one (6)

A solution of potassium hydroxide (1.12 g, 0.02 mol) in ethanol (20 mL) was added to hydrazide **3** (2.14 g, 0.01 mol). After stirring for 30 min, ethyl cyanoacetate (1.12 g, 0.01 mol) was added dropwise and the mixture was heated under reflux for 10 h. The reaction mixture was then cooled, diluted with water and acidified with conc. HCl. The resulting solid was washed with water, filtered, dried and crystallized from ethanol. White powder crystals, (1.51 g, 71 %), mp. 155–157 °C. IR (ν/cm⁻¹): 3318–3141 (NH, NH₂), 2951, 2848 (CH aliphatic), 1712 (C=O ester), 1678 (C=O), 1618 (C=C). ¹H NMR: δ 10.35 (s, 1H, NH), 6.75 (s, 2H, NH₂), 1.23–1.30 (m, 20H, CH₂ in alkyl chain), 0.91 (t, 3H, terminal CH₃). Anal. Calc. for C₁₅H₂₇N₃O₂ (281.39): C, 64.02; H, 9.67; N, 14.93 %. Found: C, 63.83; H, 9.89; N, 15.15 %.

Synthesis of N-(1,3-Dioxoisoindolin-2-yl)dodecanamide (7)

A mixture of hydrazide **3** (2.14 g, 0.01 mol) and phthalic anhydride (1.48 g, 0.01 mol) in (10 mL) glacial acetic acid was heated under reflux for 6 h. The mixture was poured into crushed ice (≈30 g) after cooling. The separated residue was washed with water, filtered, dried and crystallized from acetic acid. Colorless crystals, (1.73 g, 81 %), mp. 125–127 °C. IR (ν/cm⁻¹): 3208 (NH), 2918, 2849 (CH aliphatic), 1676 broad (C=O). ¹H NMR: δ 9.11 (s, 1H, NH), 7.58–7.90 (m, 4H, ArH), 1.30–1.40 (m, 20H, CH₂ in alkyl chain), 0.91 (t, 3H, terminal CH₃). Anal. Calc. for C₂₀H₂₈N₂O₃ (344.45): C, 69.74; H, 8.19; N, 8.13 %. Found: C, 70.01; H, 8.48; N, 8.45 %.

Synthesis of 2-Dodecanoyl-N-phenylhydrazinecarbothioamide (8)

A mixture of hydrazide **3** (2.14 g, 0.01 mol), phenyl isothiocyanate (1.35 g, 0.01 mol) in dry benzene (25 mL) was heated under reflux for 6 h. After cooling the solvent was evaporated under reduced pressure. The solid product obtained was filtered, washed with ethanol and finally crystallized from ethanol. Colorless crystals (1.79 g, 84 %), mp. 137–139 °C. IR (ν/cm⁻¹): 3411–3127 (NH), 2918, 2850 (CH aliphatic), 1666 (C=O). ¹H NMR: δ 8.75, 4.66, 4.21 (3 s, 3H, 3NH), 1.45–1.30 (m, 20H, CH₂ in alkyl chain), 0.88 (t, 3H, terminal CH₃). Anal. Calc. for C₁₉H₃₁N₃OS (349.53): C, 65.29; H, 8.94; N, 12.02; S, 9.17 %. Found: C, 65.01; H, 8.63; N, 11.77; S, 9.36 %.

Synthesis of 4-Phenyl-5-undecyl-4H-1,2,4-triazole-3-thiol (9)

A mixture of thiosemicarbazide 8 (3.49 g, 0.05 mol) and sodium hydroxide solution (1.0 g in 5 mL H_2O) in ethanol (30 mL) was heated under reflux for 4 h, then allowed to cool. The mixture was acidified with concentrated hydrochloric acid and the formed solid product was filtered, washed with water and recrystallized from ethanol. White solid, (2.65 g, 76 %), mp. 112–114 °C. IR (v/cm^{-1}): 3046 (CH aromatic), 2918, 2849 (CH aliphatic), 1597, 1574 (2C=N). ^{1}H NMR: δ 12.25 (s, 1H, SH), 7.58–7.32 (m, 5H, ArH), 1.29–1.18 (m, 20H, CH_2 in alkyl chain), 0.90 (t, 3H, terminal CH_3). ^{13}C NMR: δ 168.30, 152.72, 129.97, 129.02, 128.13, 127.72, 34.20, 31.76, 30.40, 29.44, 28.86, 26.10, 25.45, 22.75, 14.22. Anal. Calc. for $C_{19}H_{29}N_3S$ (331.52): C, 68.84; H, 8.82; N, 12.68; S, 9.67 %. Found: C, 68.56; H, 8.66; N, 12.43; S, 9.28 %.

Synthesis of N-Phenyl-5-undecyl-1,3,4-thiadiazol-2-amine (10)

Thiosemicarbazides 8 (3.49 g, 0.01 mol) was treated with concentrated sulphuric acid (5 ml) at 0 °C in an ice bath with constant stirring for 12 h. The reaction mixture was poured into ice water (50 mL). The product was precipitated, filtered and washed with excess cold water. Pale yellow solid, (1.91 g, 55 %), mp. 100–102 °C. IR (v/cm^{-1}): 3193 (NH), 2850, 2919 (CH aliphatic), 1618, 1550 (C=N). ^{1}H NMR: δ 7.92 (s, 1H, NH), 7.41–7.26 (m, 5H, ArH), 1.40–1.23 (m, 20H, CH_2 in alkyl chain), 0.88 (t, 3H, terminal CH_3). ^{13}C NMR: δ 168.33, 153.04, 133.59, 129.89, 129.06, 128.42, 127.94, 34.43, 31.79, 29.54, 29.28, 28.84, 26.03, 25.66, 22.80, 14.73. Anal. Calc. for $C_{19}H_{29}N_3S$ (331.52): C, 68.84; H, 8.82; N, 12.68; S, 9.67 %. Found: C, 69.08; H, 9.11; N, 12.46; S, 9.32 %.

Synthesis of (Z)-N′-(4-(4-Bromophenyl)-3-phenylthiazol-2(3H)-ylidene)dodecanehydrazide (11)

A solution of hydrazide 3 (2.14 g, 0.01 mol) in ethanol (40 mL), and p-bromophenacyl bromide (2.77 g, 0.01 mol) was heated under reflux for 5 h. The reaction mixture was poured on an ice-water mixture and the pH adjusted to 7 using sodium hydroxide. The solid product was collected by filtration and crystallized from ethanol. Pale yellow crystals, (1.56 g, 73 %), mp. 110–112 °C. IR (v/cm^{-1}): 3332 (NH), 2851, 2919 (CH aliphatic), 1670 (CO), 1610 (C=C), 1597 (C=N). ^{1}H NMR: δ 12.41 (s, 1H, NH), 7.58–7.29 (m, 4H, ArH), 6.58 (s, 1H, CH of thiazole ring), 1.42–1.14 (m, 20H, CH_2 in alkyl chain), 0.98 (t, 3H, terminal CH_3). ^{13}C NMR: δ 172.82, 168.09, 160.07, 142.93, 136.81, 130.14, 129.92, 128.95, 125.66, 122.61, 117.70,

99.83, 31.81, 29.64, 29.35, 28.72, 26.45, 25.33, 22.68, 14.12. Anal. Calc. for $C_{27}H_{34}BrN_3OS$ (528.55): C, 61.35; H, 6.48; N, 7.95; S, 6.07 %. Found: C, 61.53; H, 6.69; N, 7.64; S, 6.31 %.

Synthesis of N′-Benzylidenedodecanehydrazide (12)

A solution of hydrazide 3 (2.14 g, 0.01 mol) in methanol (10 mL) and aromatic aldehydes, e.g., benzaldehyde (1.06 g, 0.01 mol), was heated under reflux for 4 h, using a few drops of acetic acid. After cooling, the formed solid product was filtered, dried and recrystallized from ethanol. Yellow solid, (1.66 g, 78 %), mp. 90–92 °C. IR (v/cm^{-1}): 3187 (NH), 2915, 2847 (CH aliphatic), 1669 (C=O), 1602 (C=N). ^{1}H NMR: δ 8.83 (s, 1H, NH), 8.20 (s, 1H, CH=N), 7.85–7.29 (m, 5H, ArH), 1.46–1.28 (m, 20H, CH_2 in alkyl chain), 0.93 (t, 3H, terminal CH_3). Anal. Calc. for $C_{19}H_{30}N_2O$ (302.45): C, 75.45; H, 10.00; N, 9.26 %. Found: C, 75.69; H, 10.27; N, 9.02 %.

Synthesis of N-(4-Oxo-2-phenylthiazolidin-3-yl)dodecanamide (13)

To a stirred solution of compound 12 (3.02 g, 0.01 mol) in dry benzene (30 mL), thioglycollic acid (0.92 g, 0.01 mol) in dry benzene (5 mL) was added. The reaction mixture was heated under reflux for 10 h and the excess solvent evaporated under pressure. The obtained solid was filtered, dried and crystallized from ethanol. Pale yellow, (2.05 g, 68 %), mp. 75–77 °C. IR (v/cm^{-1}): 3260 (NH), 3026 (CH aromatic), 2918, 2850 (CH aliphatic), 1716, 1665 (C=O). ^{1}H NMR: δ 7.79 (s, 1H, NH), 7.40–7.26 (m, 5H, ArH), 4.68 (s, 1H, CH of thiazole ring), 3.66, 3.81 (2 s, 2H, CH_2 of thiazole ring), 1.46–1.28 (m, 20H, CH_2 in alkyl chain), 0.89 (t, 3H, terminal CH_3). ^{13}C NMR: δ 176.48, 167.12, 133.83, 130.47, 129.26, 128.85, 127.73, 126.00, 63.17, 41.71, 31.79, 30.77, 29.46, 29.14, 25.61, 24.86, 22.80, 18.43, 14.23. Anal. Calc. for $C_{21}H_{32}N_2O_2S$ (376.56): C, 66.98; H, 8.57; N, 7.44; S, 8.52 %. Found: C, 67.22; H, 8.78; N, 7.71; S, 8.81 %.

Synthesis of 1-(3,5-Diamino-4,5-dihydro-1H-pyrazol-1-yl)dodecan-1-one (14)

A mixture of hydrazide 3 (2.14 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) was heated under reflux in ethanol (30 mL) with a few drops of pipredine for 5 h. After cooling, the separated product was filtered, dried and recrystallized from ethanol. White yellow powder, (1.62 g, 76 %), mp. 99–101 °C. IR (v/cm^{-1}): 3314–3200 (NH_2), 2919, 2849 (CH aliphatic), 1660 (C=O), 1599 (C=N). ^{1}H NMR: δ 7.79 (s, 1H, NH), 6.78 (s, 1H, CH of diazole ring), 3.90 (s, 2H, NH_2), 2.52 (s, 2H, NH_2), 1.71 (s, 2H, CH_2 of

diazole ring), 1.30–1.27 (m, 20H, CH$_2$ in alkyl chain), 0.99 (t, 3H, terminal CH$_3$). ^{13}C NMR: δ 174.06, 152.82, 51.48, 34.61, 31.91, 29.60, 29.47, 29.33, 29.31, 29.29, 25.51, 22.69, 18.43, 14.12. Anal. Calc. for C$_{15}$H$_{30}$N$_4$O (282.25): C, 63.79; H, 10.71; N, 19.84 %. Found: C, 64.00; H, 10.93; N, 19.60 %.

Synthesis of N-(2,5-Dimethyl-1H-pyrrol-1-yl)dodecanamide **(15)**

A solution of hydrazide **3** (2.14 g, 0.01 mol) in ethanol (20 mL) and acetonyl acetone (2.28 g, 0.02 mol) with a few drops of glacial acetic acid was heated on a water bath for 5 h. After cooling, the mixture was poured into cold water and the obtained solid was filtered, washed with water, dried and crystallized from ethanol. Brown solid, (1.84 g, 86 % yield, mp. 65–67 °C. IR (ν/cm^{-1}): 3272 (NH), 2915, 2848 (CH aliphatic), 1665 (C=O), 1590 (C=C). ^{1}H NMR: δ 7.82 (s, 1H, NH), 5.85 (2 s, 2H, 2CH of pyrrole ring), 2.20 (s, 6H, 2CH$_3$), 1.40–1.26 (m, 20H, CH$_2$ in alkyl chain), 0.94 (t, 3H, terminal CH$_3$). Anal. Calc. for C$_{18}$H$_{32}$N$_2$O (292.46): C, 73.92; H, 11.03; N, 9.58 %. Found: C, 73.67; H, 10.81; N, 9.79 %.

Synthesis of 2-Undecyl-4H-1,3,4-oxadiazin-6(5H)-one **(16)**

A solution of hydrazide **3** (2.14 g, 0.01 mol) in acetic anhydride (20 mL) and chloroacetic acid (0.94 g, 0.01 mol) in the presence of sodium acetate (1.64 g, 0.02 mol) was heated under reflux for 4 h, then poured into water. A solid product was obtained by filtration and recrystallization from toluene. White solid, (1.43 g, 67 %), mp. 94–96 °C. IR (ν/cm^{-1}): 3216 (NH), 2918, 2849 (CH aliphatic), 1698 (C=O), 1598 (C=N). ^{1}H NMR: δ 8.88 (s, 1H, NH), 3.66 (s, 2H, CH$_2$ of oxadiazine ring), 1.32–1.23 (m, 20H, CH$_2$ in alkyl chain), 0.89 (t, 3H, terminal CH$_3$). ^{13}C NMR: δ 177.41, 155.72, 51.48, 31.79, 29.22, 29.16, 29.12, 29.07, 26.32, 25.19, 24.97, 22.80, 20.89. Anal. Calc. for C$_{14}$H$_{26}$N$_2$O$_2$ (254.37): C, 66.10; H, 10.30; N, 11.01 %. Found: C, 65.88; H, 10.08; N, 11.28 %.

Synthesis of 5-Undecyl-1,3,4-oxadiazole-2(3H)-thione **(17)**

Finely powdered KOH (1.12 g, 0.02 mol) was dissolved in ethanol (30 mL), and hydrazide **3** (2.14 g, 0.01 mol) was added. (0.76 g, 0.01 mol) of carbon disulfide was then slowly added and the reaction mixture was heated under reflux on a steam bath for 10 h. The concentrated solution was cooled and acidified with hydrochloric acid. The precipitated solid was filtered, washed with ethanol, dried and crystallized from ethanol. White yellow solid, (1.47 g, 69 %), mp. 81–83 °C. IR (ν/cm^{-1}): 3221 (NH), 2918, 2848 (CH aliphatic), 2640 (C=S), 1618 (C=N). ^{1}H NMR: δ 11.5

(s, 1H, NH), 1.42–1.41 (m, 20H, CH$_2$ in alkyl chain), 0.86 (t, 3H, terminal CH$_3$). Anal. Calc. for C$_{13}$H$_{24}$N$_2$OS (256.41): C, 60.89; H, 9.43; N, 10.93; S, 12.51 %. Found: C, 61.15; H, 9.66; N, 11.16; S, 12.77 %.

Synthesis of 4-Amino-5-undecyl-4H-1,2,4-triazole-3-thiol **(18)**

An ethanol solution (30 mL) of 1,3,4-oxadiazole **17** (0.01 mol) and hydrazine hydrate (0.38 g, 0.012 mol) was heated under reflux for 3 h. After cooling, the solution was poured into ice water. The resulting product was filtered, washed with water and crystallized from ethanol. White solid, (1.58 g, 62 %), mp. 94–96 °C. IR (ν/cm^{-1}): 3318, 3141 (NH$_2$), 2919, 2848 (CH aliphatic), 1618, 1570 (C=N), 1176 (SH). ^{1}H NMR: δ 11.61 (s, 1H, SH), 6.86 (s, 2H, NH$_2$), 1.41–1.30 (m, 20H, CH$_2$ in alkyl chain), 0.919 (t, 3H, terminal CH$_3$). ^{13}C NMR: δ 166.85, 156.43, 34.46, 31.92, 30.72, 29.64, 29.57, 29.35, 29.21, 28.95, 28.51, 26.17, 25.70, 25.64. Anal. Calc. for C$_{13}$H$_{26}$N$_4$S (270.44): C, 57.74; H, 9.69; N, 20.72; S, 11.86 %. Found: C, 57.55; H, 9.42; N, 20.48; S, 11.63 %.

Synthesis of 5-Undecyl-1,3,4-thiadiazole-2(3H)-thione **(19)**

Finely powdered KOH (1.12 g, 0.02 mol) was dissolved in ethanol (30 mL), and hydrazide **3** (2.14 g, 0.01 mol) was added. (0.76 g, 0.01 mol) of carbon disulfide was then slowly added over a period of 10 min and the reaction mixture stirred for an additional 1 h. The reaction mixture was then heated under reflux on a steam bath for 12 h, concentrated, cooled and acidified with diluted H$_2$SO$_4$. The solid mass that precipitated was filtered, washed with ethanol, dried and recrystallized from ethanol. Pale yellow solid, (1.51 g, 71 %), mp. 125–127 °C. IR (ν/cm^{-1}): 3225 (NH), 2919, 2848 (CH aliphatic), 2635 (C=S), 1603 (C=N). ^{1}H NMR: δ 10.75 (s, 1H, NH), 1.39–1.24 (m, 20H, CH$_2$ in alkyl chain), 0.89 (t, 3H, terminal CH$_3$). Anal. Calc. for C$_{13}$H$_{24}$N$_2$S$_2$ (272.47): C, 57.30; H, 8.88; N, 10.28; S, 23.54 %. Found: C, 57.02; H, 8.56; N, 10.43; S, 23.79 %.

Preparation of Nonionic Surface Active Agents (Schemes 3, 4)

Nonionic surface active agents were prepared by addition of propylene oxide (5 mol) to synthesized compounds 3–19. Propylene oxide was added above the melting point of each compound using KOH as catalyst [22]. The quantity of propylene oxide which reacted and the average degree of propoxylation were measured through the change in mass of the reaction mixture (increase of mixture weight after addition of propylene oxide is the average amount of propoxylation). The based catalyst was neutralized by
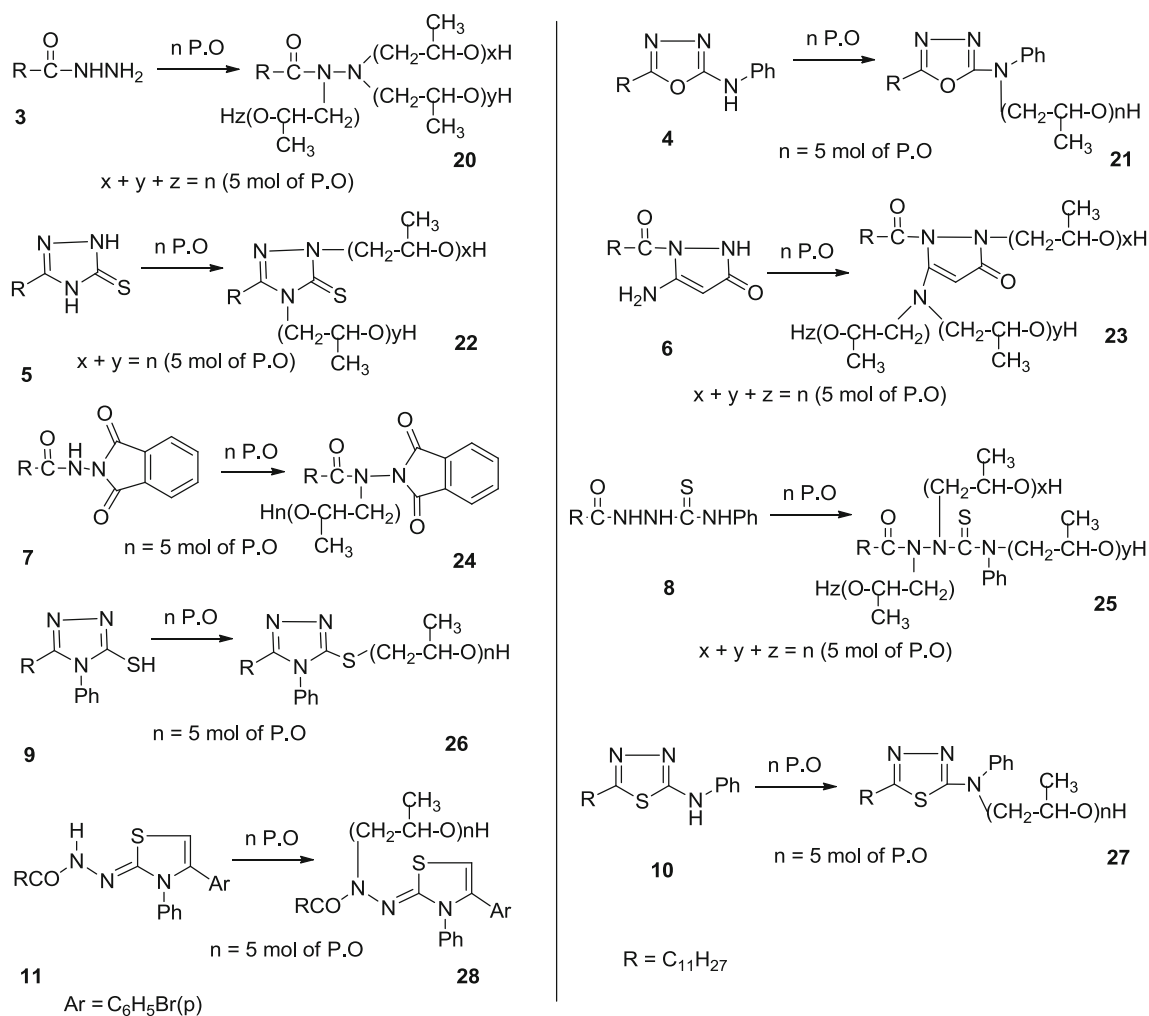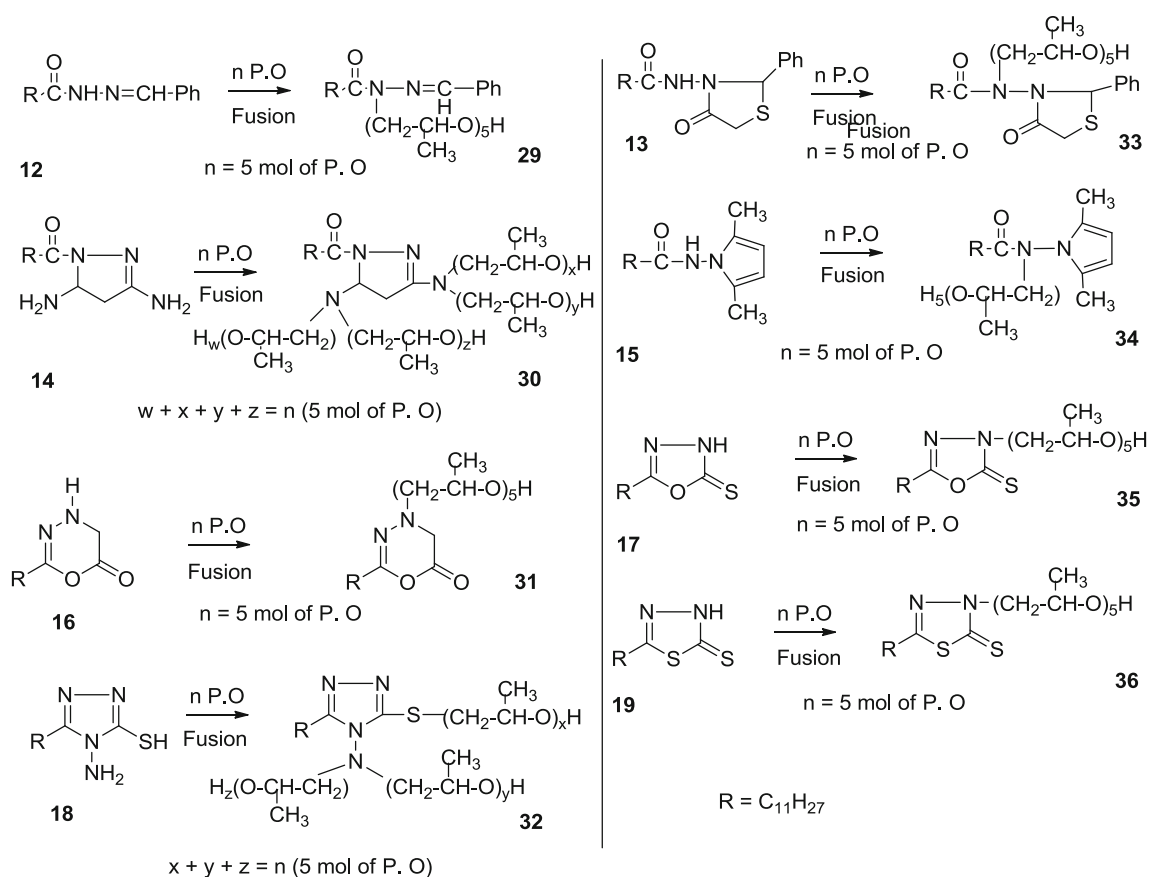
Scheme 3 Synthesis of surface active agents (20–28) from the synthesized compounds (3–11)

adding HCl to a pH of 7. Addition of propylene oxide produced mixtures of propoxylated products, and their structures were confirmed on the basis of IR and ^{1}H NMR spectra. IR spectra revealed a broad band in the region of (3500–2500) cm^{-1} (OH) and two other bands in the regions of (1100–1000) and (950–900) cm^{-1} for (C–O–C ether linkage of polypropoxy chain) besides the original bands of the starting compounds. ^{1}H NMR spectra showed the protons of the propoxy groups, which appeared as broad multiple signals in the region of (3.2–3.8), in addition to the other signals of the starting compounds.

Biological Activity

Antimicrobial activity of the prepared compounds was tested via a modified Kirby-Bauer disc diffusion method [23]. The compounds were tested against Escherichia coli and Staphylococcus aureus bacteria. The compounds were also tested against Aspergillus flavus and Candida albicans fungus. A filter-paper disk, impregnated with the compound to be tested, was placed on an agar surface. The compound diffused from the filter paper into the agar. The concentration of the compound is highest next to the disk, and decreases with increased distance from the disk. If the compound is effective against bacteria at a certain concentration, no colonies will grow where the concentration in the agar is greater than or equal to the effective concentration. This is the zone of inhibition. This, along with the rate of antibiotic diffusion, is used to estimate the bacteria's sensitivity to that particular antibiotic. In general, larger zones correlate with smaller minimum inhibitory concentration (MIC) of an antibiotic for that bacterium. Inhibition produced by the test is compared with that produced by a known concentration of a reference compound. This information can be used to choose appropriate antibiotics to combat a particular infection.

Scheme 4 Synthesis of surface active agents (**29–36**) from the synthesized compounds (**12–19**)

Surface and Interfacial Tension Measurements

Surface and interfacial tension measurements of the prepared surfactants (γ) were made at 25 °C with a Du Nouy tensiometer (Kruss K_6) [24] with a platinum ring for various concentrations of the synthesized surfactants. Paraffin oil was used for the interfacial tension measurements using aqueous surfactant solutions (0.1 wt%) at room temperature (25 °C).

Cloud Point Measurements

In a temperature-controlled bath, a 1 wt% solution of the tested compound was gradually heated until the clear or nearly clear solutions became definitively turbid [25]. The temperature was then recorded and the solution was allowed to cool down until it became clear again. The process was repeated to check the reproducibility of the recorded temperature.

Wetting Time Measurements

Wetting time was measured by immersing a cotton skein (1 g) in a 0.1 wt% solution of the prepared surfactants in distilled water at 25 °C according to the Draves technique [26]. The sinking time was measured in seconds.

Foam Measurements

A typical method in which 25 mL of the solution (1.0 wt%) was shaken vigorously for 10 s in a 100 ml graduated cylinder with glass stopper at 25 °C was used. The foam height was measured [27].

Emulsion Stability Measurements

In a 100-mL graduated, stoppered tube, an aqueous solution of the surfactant (10 mL, 20 mol) was mixed with light paraffin oil (6 mL). The mixture was shaken vigorously by magnetic stirring for 2 min at 25 °C. The formed emulsion was separated and observed. The time taken for the separation of the aqueous layer indicates the emulsion stability of the surfactant [28].

Interfacial Properties

The critical micelle concentration (CMC) is the minimum concentration at which surfactant molecules begin to form micelles [29]. CMC values were obtained through a conventional plot of the surface tension versus the concentration logarithm of the surfactant. The CMC concentration

corresponds to the point where the surfactant first shows the lowest surface tension, and after which the surface tension remains nearly constant.

The effectiveness of a certain surfactant (π_{cmc}) is expressed in terms of the decrease in the surface tension that is induced by this surfactant at the CMC [30]. The effectiveness was calculated from Eq. (1):

$$\pi_{cmc} = \gamma_0 - \gamma_{cmc} \tag{1}$$

where γ_o is the surface tension measured for the pure water at the appropriate temperature and γ_{cmc} is the surface tension at the CMC.

Efficiency (pC20)

The efficiency of a surfactant (pC20) is the negative log of the surfactant concentration required to lower the surface tension of water by 20 mN/m [31].

Maximum Surface Excess Γ_{max}

The maximum surface excess can be attained from the Gibbs Equation shown in Eq. (2):

$$\Gamma_{max} = -1/RT[d\gamma/d \log c]. \tag{2}$$

where R is the ideal gas constant, T is the absolute temperature and $d\gamma/d\log c$ is the slope of the surface tension versus $\log c$ plot at 25 °C [32].

Minimum Surface Area (A_min)

Minimum surface area (A_{min}) was calculated from Eq. (3) [33]:

$$A_{min} = 10^{16}/N\,\Gamma_{max} \tag{3}$$

where N is Avogadro's number and Γ_{max} is the maximum surface excess calculated from Eq. 2.

Biodegradability of the Synthesized Surfactants

The biodegradation tests of the synthesized nonionic surfactants were performed according to the river water Die-Away method [34] using Nile River water. In this test, a stirred solution containing the tested surfactant (1000 ppm) was incubated at 25 °C. Samples were withdrawn daily, filtered using Whatman filter paper (GE Healthcare Life Sciences) and the surface tension was measured using a Du Nouy tensiometer (Kruss type K_6). The process was repeated for seven days. The biodegradation percentage (D) was calculated in terms of the measured surface tension according to Eq (4):

$$D = \left[(\gamma^t - \gamma^0)/(\gamma^{bt} - \gamma^0)\right] \times 100 \tag{4}$$

where γ^0 is the surface tension at time zero (initial surface tension), γ^t is the surface tension at time t, and γ^{bt} is the surface tension of the blank experiment at time t (without surfactant).

Results and Discussion

Biological Activity

Investigation of the antimicrobial screening of some of the synthesized compounds (20–36) revealed that all the tested compounds showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus,* and also showed fungicidal activity on one or more of *Aspergillus flavus* and *Candida albicans* as shown in Table 1. Tetracycline and Amphotericin B were taken as a reference for antibacterial and antifungal agents, respectively. Formation of thiazole **33** and thiadiazole **36** showed an excellent activity against *Aspergillus flavus*. Thiazole **27** and thiadiazole derivative **28** exhibited good antibacterial activity. Moreover, pyrazole derivatives **23** and **30** exhibited moderate antifungal activity against *Candida albicans*. In addition, oxdiazine derivative **31** showed antibacterial and antifungal activities similar to the oxdiazole derivatives **21** and **35**. The presence of the heterocyclic moiety in the prepared nonionic surfactant molecules appears to enhance antibacterial activity.

Surface Activity Properties

Moderate foaming and good detergency are surfactant characteristics employed in a variety of ways in the leather industry [35]. The surface activity and related properties of the synthesized compounds are given in Table 2. The surface activity properties were independent of the heterocyclic moiety but depended on the hydrophobicity (C_{12}) and hydrophilicity (propylene oxide units), i.e., these compounds are used as effective emulsifying agents in many fields, such as cosmetics, formulations, pesticides, textiles, etc.

Surfactants are used in a large number of applications due to their ability to alter the energy relationships at interfaces and to lower surface and interfacial tension [36]. The surface tension results indicate surfactants **23** and **30** have the maximum ability while **21** shows the minimum ability to reduce surface tension of an aqueous system in the series of an amphiphile being reported. In addition, comparing structurally related triazole derivatives, **32** is slightly more effective in decreasing the surface tension than triazole derivatives **22** and **26**. The oxazolidine derivatives **21** and **35** induced the lowest reduction in surface and interfacial tension of the surfactants tested.

Table 1 Antimicrobial activity of some synthesized compounds

Sample	Inhibition zone diameter (mm/mg sample)							
	Escherichia coli (G$^-$)		*Staphylococcus aureus* (G$^+$)		*Aspergillus flavus* (G$^-$)		*Candida albicans* (G$^+$)	
	MIC	A	MIC	A	MIC	A	MIC	A
Control: DMSO	–	0.0	–	0.0	–	0.0	–	0.0
Tetracycline	200	31	200	30	–	–	–	–
Amphotericin B	–	–	–	–	200	16	200	19
20	400	12	400	11	400	0.0	200	7
21	400	13	400	12	400	9	400	7
22	400	13	400	7	400	8	400	8
23	200	11	200	11	200	10	200	0.0
24	400	14	400	10	400	8	400	8
25	400	14	400	13	400	10	400	8
26	400	23	400	14	400	8	400	10
27	400	16	400	15	400	11	400	0.0
28	400	17	400	16	400	10	400	0.0
29	200	10	200	11	200	7	200	0.0
30	200	11	200	10	200	0.0	200	8
31	400	13	400	12	400	9	400	7
32	200	12	400	12	400	12	400	10
33	400	13	400	12	400	14	400	6
34	400	15	200	13	200	9	200	8
35	400	13	400	12	400	9	400	7
36	400	14	400	11	400	13	400	9

A antimicrobial activity of tested compounds, *MIC* minimum inhibitory concentration, *A = 0* not active, *A > 7* mm = slighty active, *A > 15* mm = moderately active, *A > 30* mm = highly active

Table 2 Surface properties of the synthesized compounds

Compounds	Surface tension (mN/m) 0.1 wt%	Interfacial tension (mN/m) 0.1 wt%	Cloud point °C	Wetting time (sec)	Emulsion stability (min)	Foam height (mm)
20	37	10	85	155	165	75
21	44	19	70	122	145	80
22	38	12	90	98	110	65
23	36	9.5	97	120	136	66
24	40	11	80	131	111	82
25	41	12	87	104	123	70
26	38	11	100	96	106	68
27	41	13	85	112	125	55
28	38	19	80	115	133	72
29	39	12	85	130	130	48
30	36	9.5	90	113	128	40
31	39	13	86	124	119	77
32	37	8.8	>100	95	102	80
33	39	12	100	109	115	78
34	41	13.5	73	135	121	50
35	42	17	75	105	115	65
36	40	12.5	82	111	127	50

Errors of measurement were: surface and interfacial tensions = ±0.1 dynes/cm, cloud point = ±1 °C, foam height = ±2 mm, wetting time = ±1 s, emulsion = ±1 min

Cloud Point

For nonionic surfactants, a common and characteristic observation is that they exhibit reverse solubility versus temperature behavior in water. The cloud point is a critical factor in the performance of nonionic surfactants; generally, nonionic surfactants show optimal effectiveness when used near or below their cloud point. The cloud point depends on the chemical structure [37, 38]. The results (Table 2) show that surfactants **26** and **32** have the maximum cloud point while amphiphile **21** has the minimum cloud point in the series of amphiphiles being reported. These results suggest that these surface-active compounds can be used over a wide range of temperatures.

Wetting Time

In the present work, the efficiency of the synthesized surfactants as wetting agents was measured according to the Draves technique [26], which measures the ability of a surfactant solution to displace air from a weighted skein of cotton by spread wetting. Shorter wetting times indicate more efficient wetting. Surfactants **20–36** demonstrated varying wetting abilities depending on the chemical structure, as indicated in Table 2. Surfactants **26** and **32** exhibited the shortest sinking time, and, consequently, are the most efficient wetting agents among the studied group.

Foaming Properties

The foaming ability of the synthesized surfactants was examined using the Ross Miles method [27]. As indicated in Table 2, surfactants **29** and **32** showed the least foaming. In generally, all of the synthesized surfactants have relatively low foam. Addition of PO groups to a surfactant usually lowers the foam due to a decrease in the cloud point. Branching in the headgroup also limits close packing of molecules at the air/water interface necessary to stabilize the foam lamella.

Emulsion Stability

Studies are still being carried out on the utilization of surfactants in emulsion formulation, which is of immense importance to technological development. In many textile processes, such as scouring and dyeing, it is necessary to add surfactants to the bath in order to remove oily impurities from the fibers. The emulsifying power of the prepared surfactants in terms of time needed for the separation of 9 mL of the solution is presented in Table 2. Generally, the measured time ranged between 102 and 165 min, thus, indicating moderate emulsifying properties for the synthesized surfactants. The moderate emulsion stability may mean a co-surfactant may be required to stabilize emulsions with these surfactants.

Critical Micelle Concentration

The CMC is a measure of surfactant efficiency as it indicates the amount of a surfactant required to reach maximum surface tension reduction. A surfactant having a low CMC value enjoys excellent wetting, emulsifying, solubilizing, and detergency properties [39]. Within a given series of structurally related surfactants, factors that lead to a decrease in the surface tension are expected to decrease the CMC value. As shown in Table 3, the synthesized surfactants **23** and **33** have the lowest CMC values, which can be attributed to lower solubility of the surfactant molecules.

Effectiveness (π_{cmc})

The maximum reduction in surface tension caused by the dissolution of amphiphilic molecules is a measure of its effectiveness (π_{cmc}) [40, 41]. π_{cmc} of the synthesized surfactants is the difference between the surface tension of distilled water and that at the CMC values The synthesized surfactants **31** and **35** have the greatest ability to reduce surface tension of the aqueous system, as shown in Table 3. Logically, the effectiveness of the prepared surfactants decreases as γ_{cmc} increases.

Efficiency (pC20)

Efficiency of adsorption (pC20) is defined as the negative log of the surfactant concentration required to lower the surface tension of water by 20 mN/m. pC20 values are useful for comparing the efficiency of adsorption of a surfactant at the air/water interface [42]. The larger the pC20, the more efficiently the surfactant is adsorbed at the interface and the more efficiently it reduces the surface tension. pC20 values for the investigated surfactants are given in Table 3. In general, all of the synthesized compounds show good efficiency. The results indicate that surfactant 29 has the highest adsorption efficiency. The lowest pC20 value was observed for **23**.

Maximum Surface Excess (Γ_{max})

The extent of surfactant adsorption at a liquid surface is expressed in terms of its surface excess concentration

Table 3 Surface activity parameters for the synthesized compounds

Compounds	CMC (mmol/L)	γ_{cmc} (mN/m)	pC20	Γ_{max} (mol/m^2)	A_{min} Å^2	π_{cmc} (mN/m)
20	1.28	40.3	2.5	3.94×10^{-6}	42.14	32.70
21	1.70	44.0	2.6	3.58×10^{-6}	46.37	29.00
22	2.30	42.0	3.8	2.60×10^{-6}	63.85	31.00
23	0.90	38.0	2.1	4.71×10^{-6}	35.25	35.00
24	1.80	43.5	3.5	2.01×10^{-6}	82.20	30.50
25	1.90	44.0	2.6	4.61×10^{-6}	36.01	29.00
26	1.20	41.0	2.8	2.78×10^{-6}	59.72	32.00
27	1.30	41.0	3.4	2.11×10^{-6}	78.68	32.00
28	2.70	40.9	3.8	4.00×10^{-6}	41.46	32.00
29	1.50	36.0	4.4	3.20×10^{-6}	51.80	40.00
30	1.30	37.5	2.75	4.18×10^{-6}	39.72	35.50
31	2.10	46.0	2.7	4.04×10^{-6}	41.10	27.00
32	1.50	41.5	2.2	5.04×10^{-6}	32.94	31.50
33	0.90	40.8	3.1	2.02×10^{-6}	82.19	32.20
34	1.60	43.7	2.5	3.58×10^{-6}	46.25	29.30
35	1.92	46.0	2.2	8.07×10^{-6}	20.57	27.00
36	1.44	42.5	2.4	3.83×10^{-6}	43.35	30.50

Error of measurements was: CMC = ±0.02 mol/L, γ_{cmc} = ±0.1 mNm^{-1}, pC20 = ±1, Γ_{max} = ±0.01 mol/m, A_{min} = ±0.02 Å^2, π_{cmc} = ±0.01mNm^{-1}

Table 4 Biodegradability of prepared surfactants

Sample	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
20	37	43	55	67	79	88	94
21	44	49	57	66	75	84	91
22	38	41	44	45	59	73	89
23	36	45	57	70	88	93	–
24	40	48	56	69	80	91	–
25	41	52	63	71	80	89	93
26	38	48	59	66	78	90	–
27	41	47	53	61	70	88	94
28	38	42	44	57	76	87	93
29	39	42	46	58	71	85	94
30	36	43	56	68	79	90	–
31	39	47	55	64	76	86	92
32	37	45	58	71	87	90	–
33	39	47	58	67	79	89	96
34	42	48	57	66	77	86	95
35	40	46	52	64	71	83	90
36	41	46	52	60	72	83	89

[a] Error of calculation for the biodegradation rate = ±0.5 %

(Γ_{max}) which is defined as the excess surfactant present per unit area of surface over the bulk concentration. The surface excess depends on the molecular structure. A larger area per molecule indicates that the molecules are less tightly packed at the air/water interface [43]. The results given in Table 3 indicate that the consequential increase of Γ_{max} leads to a decrease in A_{min} values.

Minimum Surface Area (A_{min})

The minimum area per surfactant molecule A_{min} at the air/water interface at surface saturation provides information about the degree of packing and the orientation of the adsorbed surfactant molecule [44]. The calculated average areas A_{min} are given in Table 3. In general, most of the

synthesized surfactants have low A_{min} values, indicating tight packing at the interface. Surfactants **32** and **35** have the lowest A_{min} values.

Biodegradability

Biodegradation is the destruction of a chemical by the metabolic activity of microorganisms. Since surfactants are susceptible to biodegradation and, in order to examine their effect on water pollution, the biodegradability of the synthesized compounds was evaluated. Biodegradation was evaluated by the conventional River Die-Away test employing the surface-tension technique as an analytical tool [45, 46]. The biodegradability data are presented in Table 4. Within experimental accuracy, all the prepared nonionic surfactants seem to be easily degraded. In general, all of the surfactants show 40–50 % biodegradation within the first day. With 7 days, all of the surfactants showed greater than 90 % degradation.

Conclusion

A new class of nonionic surface active agents containing heterocyclic moieties were synthesized. All the new nonionic surfactants displayed good surface activity properties that are affected by the size of the hydrophilic group. In general, all of the surfactants show low foaming potential and relatively short wetting times. The lower the CMC values and the higher the Γ_{max}, the higher the emulsion stability for light paraffin oil. In addition, the synthesized surfactants showed good biodegradability within seven days.

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