Synthesis of Five and Six-Membered Heterocycles Using Activated Nitriles for Industrial Applications

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Abstract: The aim of this study is a synthesis of new bioactive heterocyclic compounds incorporated fatty chain for use in different industrial applications. Cyanoacetamide derivative (2) was successfully transferred into five and six membered heterocyclic derivatives by the reaction with various chemical reagents. Addition number of moles of propylene oxide to these compounds gave nonionic surface-active agents having a good solubility, biodegradability and hence lowers the toxicity to human beings and becomes environmentally friendly. The antimicrobial and surface activities were investigated that showed the most of them have pronounced activity, which makes them suitable for diverse applications like the manufacturing of drugs, pesticides, emulsifiers, cosmetics, etc.

Key words: synthesis, heterocyclic derivatives, surface, antimicrobial activities

1 INTRODUCTION

Cyanoacetamide derivatives are highly reactive and extensively utilized as reactants or reaction intermediates due to CO and CN groups of these compounds, which are suitably situated to enable reactions with common active reagents to form a variety of heterocyclic moieties. In addition, the active methylene group of these compounds can take part in a variety of condensation and substitution reactions1). Moreover, these compounds are versatile and convenient intermediates in organic synthesis for heterocyclic nucleus and have generated a great deal of attention due to their interesting biological, therapeutic value and their pharmaceutical activities2–7). Pyrazole, thiazole and triazole derivatives are interesting groups, which possess a widespread pharmacological properties such as antipyretic and analgesic activities8–11). Uses of these compounds for synthesis of the surface active agents have become very important in different fields due to they have been found to have double functions as better surface and biological properties compared to conventional surfactants and considered as one of the pharmaceutical and cosmetic applications due to their low toxicity and rapid biodegradation12, 13).

Organic fatty compounds are environmentally friendly, renewable and biodegradable natural materials, which play an important role in many industries due to their wide-ranging properties and their ability to be relatively easily machined and formed as plastics, foams and elastomers14). Surfactants are important class of chemicals widely used extensively for various field applications, which are considered to be a key ingredient in cleaning agents, petrochemical and modern industry including drilling, completion, refining, stimulation, enhanced oil recovery15–17). The surfactants act as emulsifier18), interfacial tension reducer19), and wetting agent20). Conventional surfactants have a long-chain hydrocarbon joined to a polar head group21). Nonionic surfactants are increasingly becoming more important since they are soluble in water and many organic solvents, and they are compatible with many other types of surfactants22). Moreover, these compounds used for the control of the optoelectronic properties of fullerene nanostructures and showed enhanced electrochemical supercapacitance performance with long cyclic stability demonstrating the potential of the materials in supercapacitor device fabrication23).

These observations and our interest in the chemistry of heterocycles24–28) prompted us to synthesize various nonionic surface active agents containing pyrazole, thiazole, triazole, thiophene, pyridine and pyridazine nucleus using fatty compounds. Propoxylation of these compounds leading to formation of new class of bioactive nonionic surface agent, which possessing higher surface activity. In addition, biological and surface activities were investigated.

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2 EXPERIMENTAL

All melting points are uncorrected and determined by the open capillary method using a Gallenkamp melting point apparatus. The infrared spectra of were recorded on BRUKER- FT/IR instrument as KBr disc. In addition, 1HNMR spectra were recorded with BRUKER AC400 spectrometer (Fällanden, Switzerland) operating at 400 MHz and the chloroform (CDCl 3 ) was used as a solvent. While, the elemental analysis was determined through CHNS elemental analyzer model EA3000 EURO VECTOR instruments. Moreover, the measurements of surface properties were carried out using Du Nouy tensiometer (Kruss Type 8451) at 25°C and the biological activity were investigated at Microbiology Department Faculty of Applied Science, Umm Al-Qura University, Kingdom of Saudi Arabia.

2.1 Synthesis of compounds

2.1.1 Synthesis of N-octadecyl-2-oxo-6-phenyl-2H-pyran-3-carboxamide (4)

A mixture of 2 (0.67 g, 2 mmol) and 3-((dimethylamino)-1-phenylprop-2-en-1-one (3) (0.35 g, 2 mmol) in ethanol (25 mL) with acetic acid (1 mL) was heated under reflux for 3 h. After cooling, the solid formed was collected by filtration and recrystallized from ethanol as yellow crystals, yield (0.42 g, 63%), m.p. 117-119°C. IR (γ/cm -1 ): 3289 (NH), 2916, 2848 (aliphatic CH), 1710, 1683 (CO amide). 1HNMR (δ, ppm): 0.89 (t, J = 7.8 Hz, 3H, terminal CH 3), 1.27-1.99 (m, 34H, 17CH 2 of alkyl chain), 6.21 (d, J = 8.2 Hz, 1H, pyrone H-5), 7.26-7.71 (m, 5H, ArH), 8.36 (s, 1H, NH), 8.71 (d, J = 8.2 Hz, 1H, pyrone H-4). Anal. Calc’d. (%): for C 30 H 45 NO 3 : C, 66.04; H, 9.74; N, 12.89; S, 7.38. Found: C, 66.44; H, 9.83; N, 12.77; S, 7.49.

2.1.2 Synthesis of 6-amino-1-octadecyl-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (5)

A solution of 2 (0.67 g, 2 mmol) in ethanol (20 mL) containing piperidine (0.3 mL), and 2-benzylidenemalononitrile (0.3 g, 2 mmol) was heated under reflux for 4 h, and then left to cool. The solid product was collected by filtration and recrystallized from ethanol as brown crystals, yield (0.43 g, 65%), m.p. 128-130°C. IR (γ/cm -1 ): 3342, 3225 (NH), 2916, 2848 (aliphatic CH), 2225 (CN), 1676 (CO). 1HNMR (δ, ppm): 0.88 (t, J = 8.1 Hz, 3H, terminal CH 3), 1.26-1.98 (m, 34H, 17CH 2 of alkyl chain), 7.28-7.78 (m, 5H, ArH), 8.26 (s, 2H, NH 2 )). Anal. Calc’d. (%): for C 24 H 32 N 4 O (448.71): C, 76.19; H, 9.07; N, 11.46. Found: C, 76.27; H, 9.15; N, 11.55.

2.1.3 Synthesis of 3,5-dimino-4-cyano-N-octadecylthiophene-2-carboxamide (6)

To a solution of 2 (0.67 g, 2 mmol) in 1,4-dioxane (20 mL) containing triethylamine (0.5 mL), malononitrile (0.13 g, 2 mmol) was added, followed by addition of an equimolar amount of elemental sulfur (0.06 g, 2 mmol). The reaction mixture was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice/water mixture con-
2.1.7 Synthesis of \( N^5 \)-octadecyl-1-phenyl-1H-pyrazole-3,5-diamine (10)

To a solution of 2 (0.67 g, 2 mmol) in ethanol (25 mL) and acetic acid (10 mL), phenyl hydrazine (0.2 g, 2 mmol) was added. The reaction mixture was heated under reflux for 5 h. The reaction mixture was poured onto ice/water mixture and then collected by filtration, and recrystallized from 1,4-dioxane as orange crystals, yield (0.47 g, 70%); m.p. 137-139°C. IR (\( \gamma/cm^{-1} \)): 3314-3200 (NH, NH), 3046 (CH aromatic), 2917-2849 (CH aliphatic), 1597 (C = C), 1574 (C = N). \( ^1 \)HNMR (\( \delta \), ppm): 0.88 (t, \( J = 8.4 \) Hz, 3H, terminal CH\(_3\)), 1.26-1.98 (m, 34H, 17CH\(_3\) of alkyl chain), 5.56 (s, 1H, NH), 6.40 (s, 1H, NH), 7.28-7.73 (m, 6H, ArH and CH = CH). Anal. Calcd. (%) for \( C_{28}H_{46}N_4O_4 \): C, 76.14; H, 10.87; N, 13.09. Found: C, 76.00; H, 10.87; N, 13.13. Found: C, 76.14; H, 10.98; N, 13.26.

2.1.8 Synthesis of ethyl 2,4-diamino-5-(octadecycarboxamido)thiophene-3-carboxylic acid (11)

To a solution of 2 (0.67 g, 2 mmol) in ethanol (50 mL) containing triethylamine (0.2 g, 2 mmol) and/or phenyl isothiocyanate (0.27 g, 2 mmol) with elemental sulfur (0.02 g, 2 mmol) were added. The reaction mixture was heated under reflux for 8 h, and then poured onto ice/water. The formed product was collected by filtration and recrystallized from ethanol as brown crystals, m.p.: 135-137°C. The reaction mixture was poured onto ice/water mixture, and then collected by filtration, and recrystallized from a water containing few drops of hydrochloric acid. The solid obtained was collected by filtration, and recrystallized from 1,4-dioxane/dimethyl for- manide as reddish yellow crystals, m.p. 130-132°C, yield: (0.59 g, 70%). IR (\( \gamma/cm^{-1} \)): 3381, 3219, 3138 (2NH, NH), 3046 (CH aromatic), 2918, 2849 (CH aliphatic), 1667 (CO). \( ^1 \)HNMR (\( \delta \), ppm): 0.63 (t, \( J = 8.4 \) Hz, 3H, terminal CH\(_3\)), 1.26-1.75 (m, 34H, 17CH\(_3\) of alkyl chain), 6.25 (s, 2H, NH), 7.03-7.71 (m, 6H, ArH and NHCO). 9.04 (s, 1H, NH of pyrazole ring). Anal. Calcd. (%) for \( C_{25}H_{28}N_4O_3 \): C, 73.96; H, 10.20; N, 12.32. Found: C, 73.80; H, 10.03; N, 12.11.

2.1.11 Synthesis of 1-acetyl-3-(octadecylamino)-5-phe- nyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (14)

An equimolar amount of 12 (0.85 g, 2 mmol) and hydra- zine hydrate (0.5 mL) was dissolved in acetic acid (30 mL), and then heated under refluxed for 6 hr. The reaction mixture was concentrated to dryness under reduced pressure, followed by separated off, washed with ethanol and purified by recrystallization for ethanol as pale yellow crystals, m.p.: 133-135°C, yield (0.53 g, 63%). IR (\( \gamma/cm^{-1} \)): 3216 (NH), 3050 (CH aromatic), 2918, 2850 (CH aliphatic), 2205 (CN), 1669 (CO); \( ^1 \)HNMR (\( \delta \), ppm): 0.88 (t, \( J = 8.1 \) Hz, 3H, terminal CH\(_3\)), 1.26-1.55 (m, 34H, 17CH\(_3\) of alkyl chain), 1.97 (s, 3H, COCH\(_3\)), 4.62 (d, \( J = 7.2 \) Hz, 1H, H-4 pyrazole), 5.42 (d, \( J = 7.0 \) Hz, 1H, H-5 pyrazole), 6.97-7.77 (m, 6H, ArH and NH). Anal. Calcd. (%) for \( C_{26}H_{28}N_4O_3 \): C, 74.95; H, 10.06; N, 11.65. Found: C, 74.83; H, 10.21; N, 11.81.

2.1.12 Synthesis of 4-cyano-3-(octadecylamino)-5-phe- nyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (15)

A mixture of 12 (0.85 g, 2 mmol) and thiosemicarbazide (0.18 g, 2 mmol) was dissolved in ethanol (25 mL) with the presence of sodium (0.2 g) and heated under reflux for 5 h. The reaction mixture was poured into ice/acidiﬁed water. The precipitate formed was washed with water, dried and puriﬁed by recrystallization from ethanol as yellow crystals, m.p. 142-144°C, yield: (0.46 g, 55%). IR (\( \gamma/cm^{-1} \)): 3314-3200 (NH, NH), 3046 (CH aromatic), 2919, 2849 (CH aliphatic), 2208 (CN); \( ^1 \)HNMR (\( \delta \), ppm): 0.88 (t, \( J = 8.4 \) Hz, 3H, terminal CH\(_3\)), 1.26-1.98 (m, 34H, 17CH\(_3\) of alkyl chain), 4.32 (d, \( J = 7.6 \) Hz, 1H, H-4 pyrazole), 5.53 (d, \( J = 7.4 \) Hz, 1H, H-5 pyrazole), 6.34 (s, 2H, NH), 7.28-7.73 (m, 6H, ArH and NH). Anal. Calcd. (%) for \( C_{27}H_{28}N_4S_4 \): C, 69.97; H, 9.52; N, 14.07; S, 6.44. Found: C, 69.79; H, 9.72; N, 14.25; S, 6.29.

2.1.13 Synthesis of 1E)-2-(octadecylamino)-2-oxo-N'- phenylacetohydrazonoyl cyanide (16)

To a cold solution of 2 (0.67 g, 2 mmol) in ethanol (20 mL) containing sodium acetate (3.0 g) phenyl diazonium salt (0.2 g, 2 mmol) was added with continuous stirring for 2 h. The formed solid was collected by filtration and recrystallized from ethanol as orange crystals, yield (0.47 g, 70%), m.p. 142-144°C. IR (\( \gamma/cm^{-1} \)): 3365, 3194 (2 NH), 2918, 2849 (CH aliphatic).
2.1.14 Synthesis of 4-(octadecylamino)-6-oxo-1-phenyl-1,6-dihydropyridazine-3,5-dicarbonitrile (17)

A mixture of 16 (0.88 g, 2 mmol) and ethyl cyanoacetate (0.3 mL, 2 mmol) in ethanol (25 mL) containing piperidine (0.1 mL) was heated under reflux for 4 h. The solid formed during reflux was collected by filtration and purified by recrystallization from ethanol as yellow crystals, yield (3.5 g, 60%). m.p: 130-132°C. IR (v/cm⁻¹): 3322 (NH), 2916, 2848 (aliphatic CH₃), 2209, 2197 (CN), 1671 (CO). δH NMR (δ, ppm): 0.80 (t, J = 7.8 Hz, 3H, terminal CH₃), 1.21-1.72 (m, 34H, 17 CH of alkyl chain), 1.79-7.78 (m, 5H, ArH), and 8.22 (s, 1H, NH). Anal. Calcd. (%) for C₃₀H₄₆N₆O₁: C, 73.58; H, 8.85; N, 14.30. Found: C, 73.74; H, 8.73; N, 14.47.

2.1.15 Synthesis of 2,4-diamino-1-octadecyl-6-oxo-5-(phenyldiazenyl)-1,6-dihydropyridine-3-carbonitrile (18)

To a solution of 16 (0.88 g, 2 mmol) in ethanol (25 mL) and dimethylformamide (5 mL) containing triethylamine (1.00 mL), malononitrile (0.13 g, 2 mmol) was added. The reaction mixture was heated under reflux for 5 h. After cooling, the reaction mixture was poured onto ice/water containing few drops of hydrochloric acid. The solid formed was filtered off and recrystallized from ethanol/dimethylformamide as pale orange crystals, m.p: 151-153°C, yield (0.74 g, 84%). IR (v/cm⁻¹): 3336-3210 (2NH), 3054 (CH aromatic), 2916-2848 (CH₃), 2223 (CN), 1675 (CO), 1608 (C = C), 1447 (N = N). δH NMR (δ, ppm): 0.89 (t, J = 8 Hz, 3H, terminal CH₃), 1.19-1.66 (m, 34H, 17 CH of alkyl chain), 6.33, 6.69 (2s, 4H, 2NH), 7.22-7.64 (m, 5H, ArH). Anal. Calcd. (%) for C₃₀H₄₆N₆O (506.73): C, 71.11; H, 9.15; N, 16.58. Found: C, 71.29; H, 9.35; N, 16.77.

2.1.16 Synthesis of N¹-octadecyl-4-(phenyldiazenyl)-1H-pyrazole-3,5-diamine (19)

A mixture of 16 (0.88 g, 2 mmol) in 1,4-dioxane (20 mL) and hydrizine hydrate (1.0 mL, 5 mmol) was refluxed for 6 h, and then allowed to cool. The solid obtained was filtered, dried and recrystallized from 1,4-dioxane as yellow crystals, yield (0.95 g, 40%), m.p 132-134°C. IR (v/cm⁻¹): 3387-3200 (2NH, NH), 2917-2849 (aliphatic CH), 1612 (C = C), 1597 (C = N), 1444 (N = N). δH NMR (δ, ppm): 0.86 (t, J = 8.3 Hz, 3H, terminal CH₃), 1.21-1.46 (m, 34H, 17 CH of alkyl chain), 5.26 (s, 2H, NH), 7.21-7.80 (m, 5H, ArH), 8.04 (s, 1H, NH), 9.55 (s, 1H, NH). Anal. Calcd. (%) for C₃₀H₄₆N₆O (454.69): C, 71.32; H, 10.20; N, 18.48. Found: C, 71.51; H, 10.38; N, 18.70.

2.1.17 Synthesis of 5-amino-N-octadecyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide (20)

A mixture of 16 (0.88 g, 2 mmol) and hydroxylamine hydrochloride (0.2 g, 3 mmol) in DMF (20 mL) with the presence of anhydrous sodium acetate (1 g) was heated under reflux for 5 h, and then, the reaction mixture was cooled to room temperature and poured onto ice/water. The formed solid was collected by filtration washed with water and recrystallized from ethanol/dimethylformamide as pale yellow crystals, yield (0.6 g, 68%), m.p: 114-116°C. IR (v/cm⁻¹): 3439-3187 (NH and NH₂), 2916-2848 (aliphatic CH), 1677 (CO) and 1599 (C = N). δH NMR (δ, ppm): 0.89 (t, J = 8.2 Hz, 3H, terminal CH₃), 1.19-1.66 (m, 34H, 17 CH of alkyl chain), 6.33 (s, 2H, NH), 7.22-7.88 (m, 5H, ArH), 8.19 (s, 1H, NH). Anal. Calcd. for C₃₀H₄₆N₆O (455.68): C, 71.17; H, 9.95; N, 15.37. Found: C, 71.32; H, 9.78; N, 15.55.

2.2 Preparation of nonionic surfactants from the synthesized heterocyclic compounds

The hydrophobe of synthesized compounds containing 0.5% KOH was stirred and heated to above its melting points, in each case, while passing a slow stream of nitrogen through the system to flush out oxygen. Nitrogen addition was stopped and propylene oxide was added drop-wise with continuous stirring and heating under efficient reflux system to retain propylene oxide. The reaction was conducted for different intervals of time ranging from 1-10 hr. The apparatus was then filled with nitrogen, cooled and reaction vessel weighted. The amount of propylene oxide, which was reacted, and the average degree of propoxylated were determined through the increment in mass of the reaction mixture (increase in weight of the mixture after the addition of propylene oxide is the average amount of propoxylated) ³⁰. The IR-spectra revealed a broad band in the region of (3500-3250) cm⁻¹ (ν OH) and two other bands in the region of (1185-1070) and (965-896) cm⁻¹ for (C–O=C ether bond of polypropoxy chain). δH NMR spectra showed that the propoxy groups protons appear as broad multiple signals in the range between (3.1-3.9 ppm), in addition to other signals of these compounds.
was gradually heated until the clear or nearly clear solution became definitely turbid. The temperature was 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.

2.3.3 Wetting time

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

2.3.4 Foaming properties

Foam height was measured according to the method. A solution of the surfactant (1.0 wt %, 25 mL) was shaken vigorously for 10 seconds in a graduated cylinder with glass stopper at 25°C. The solution was allowed to stand for 30 seconds, and then, the foam height was measured.

2.3.5 Emulsion stability

An aqueous solution of the surfactant (10 mL, 20 mol) was mixed with light paraffin oil (6 mL) in graduated stoppered tube. The mixture was shaken vigorously for 2 min at 25°C. The tube was placed upright and the separation of the formed emulsion was observed. The time taken for the separation of (9 mL) of the aqueous layer indicates the emulsion stability of the surfactant.

2.4 Biodegradability

The biodegradation tests of the surfactants were performed according to the river water die-away method. A stirred solution of the surfactant (1,000 ppm) was incubated at 25°C, the samples were withdrawn daily filtered using Whatman filter paper and the surface tension was measured using a Du-Nouy tensiometer (Kruess type Kt). This process was repeated for 8 days. The biodegradation percentage D% was calculated in terms of the measured surface tension according to the following relation. 

\[ D = \left( \gamma_t - \gamma_0 \right) \times 100 \]

where \( \gamma_t = \) surface tension at time t, \( \gamma_0 = \) surface tension at zero time, \( \gamma_t = \) surface tension of blank experiment at time t (without samples).

2.5 Biological activity

Some of the synthesized compounds were screened in vitro against some bacteria as *Staphylococcus aureus*, *Escherichia coli* and fungi as *Candida albicans* as revealed from their MIC values (125-250 mg/mL).

2.5.1 Antibacterial studies

Filter paper disc method was used for testing the antibacterial activity of all the target compounds and standard doxycycline media with DMSO was set up as control. On nutrient agar, all cultures were systematically maintained and incubated overnight at 37°C. At 1000 rpm the culture was centrifuged, pellets were suspended and then diluted in sterile normal saline solution (NSS) to obtain viable 10² cfu/mL. On nutrient agar plates, approximately 0.1 mL of diluted bacterial culture suspension was spread uniformly with the help of spreader. Sterile 8 mm discs (Hi-media Pvt. Ltd) were impregnated with the test compounds. The disc was placed on the nutrient agar plate. Each plate had one control disc impregnated with the solvent. The plates were then incubated for 24 h at 37°C, and the resulting zones of inhibition were measured (mm).

2.5.2 Antifungal studies

The test compounds were dissolved in DMSO and the media with DMSO was set up as control. All cultures were consistently maintained on SDA (sabouraud’s dextrose agar) and incubated at 28°C. Spore formation of filamentous fungi was prepared from 7 day old culture in sterile normal saline solution (8% NaCl) and approximately diluted to obtain 10⁵ cfu/mL. The inoculums of non-sporing fungi, *Candida albicans* were performed by growing the culture in SD (sabouraud’s) broth at 37°C for overnight. At 1000 rpm the culture was centrifuged, pellets were suspended and then diluted in sterile normal saline solution (NSS) to obtain viable 10⁷ cfu/mL. On SDA plates, approximately 0.1 mL of diluted fungal culture suspension was spread uniformly with the help of spreader. Sterile 8 mm discs (Hi-media Pvt. Ltd) were impregnated with the test compounds. The disc was placed onto the SDA plate. Each plate had one control disc impregnated with the solvent. The plates for *Candida albicans* plates were incubated at 37°C for 18-48 h. Antifungal activity was determined by measuring the diameters of the inhibition zone (mm).

3 RESULTS AND DISCUSSION

3.1 Synthesis

Heating of octadecyl amine 1 with ethyl cyanoacetate gave 2-cyano-N-octadecylacetamide (2) in good yield according to ref. The presence of CN group adjacent to active methylene group in α-position of ketone group causing the high efficiency of cyanoacetamide 2 towards variety nucleophiles via nucleophilic cycloaddition reactions. Thus, the reaction of 2 with enamino acid derivative 3 in boiling ethanol with few drops of acetic acid gave the pyran derivative 4. The structure of 4 was established by elemental analysis and spectroscopic data, which agree with the assigned structure. The IR spectrum of 4 confirmed that CN group involved in the cyclization reaction, where it devoid of an absorption band for the CN group but showed absorption band at 1710 cm⁻¹ for (CO amide). Also, the reaction of arylidene malononitrile with acetamide 2 in ethanol with a catalytic amount of piperidine delivered the pyridine derivative 5. The reaction mechanism was supposed to proceed via the initial Michael addition of the methylene group to the double bond of the arylidene derivative to form the non-isolable Michael adduct, which cyclized to afford the pyridine derivative 5. In addition, when the acetamide 2 was reacted with elemental...
sulfur and malononitrile gave thiophene derivative 6. Moreover, the reaction of acetamide 2 with malononitrile in ethanol containing a few drops of piperidine led to formation of pyridine derivative 7. The data of spectra for the products showed agreement with the proposed structure (see experimental part).

On the other hand, tetrahydrobenzo[b]thiophene derivative 8 could be achieved by the reaction of acetamide 2 with cyclohexanone and sulfur in boiling ethanol containing a few drops of morpholine. The IR spectrum of 8 showed the absence of any peak in the district 2000-2250 cm\(^{-1}\) for CN group but displayed absorption bands at 3378-3187 cm\(^{-1}\) assignable to NH and NH\(_2\) groups that confirm that the CN group was included in the reaction. Similarly, the formation of thiazole derivative 9 was achieved via the reaction of acetamide 2 with thioglycolic acid in boiling pyridine. The IR spectrum of 9 revealed that the absence of any absorption band in the region of 2150-2250 cm\(^{-1}\) for CN group, which confirm that cyano group was involved in a cycloaddition reaction. Moreover, the pyrazole derivative 10 was obtained in good yield via the reaction of acetamide 2 with phenylhydrazine in refluxing ethanol containing a few drops of acetic acid. Furthermore, the acetamide 2 was allowed to react with ethyl cyanoacetate and elemental sulfur in boiling ethanol containing a few drops of triethylamine to produce the thiophene derivatives 11 (Scheme 1). The structure of 11 was confirmed from its IR spectrum that indicated the absence of CN absorption band and contains the characteristic absorption bands for amino and carbonyl functional groups.

The work was extended to shed more light on the reactivity of acetamide 2 as bifunctional reagent toward other reagents. Thus, the chalcone 12 was synthesized through condensation of acetamide 2 with benzaldehyde in boiling ethanol with a few drops of piperidine. The IR spectrum of chalcone 12 revealed absorption bands at 1670, 2197, and 3332 cm\(^{-1}\) corresponding to CO, CN and NH groups, respectively. While the \(^1\)HNMR spectra showed the absence of the active methylene proton and showed signals at \(\delta\) 7.69 ppm for N-CH proton and signal at \(\delta\) 8.27 assigned to the NH proton. As an extension of this synthetic route, the behavior of chalcone 12 toward some reagents was investigated. Thus, refluxing of chalcone 12 with hydrazine hydrate in ethanol afforded pyrazole derivative 13. The reaction involves \(\beta\)-attack on the C(=O)C=C moiety in chalcone 12 with subsequent 1,5-intramolecular dipolar cyclization and concomitant aromatization. Also, N-acetyl pyrazole derivative 14 was prepared by heating of chalcone 12 with hydrazine hydrate in boiling acetic acid. In addition, upon using basic media, the pyrazole derivative 15 was obtained by heating of thiosemi-carbazide with chalcone 12 in ethanolic NaOH solution. The structure of pyrazole derivatives 13-15 was characterized using elemental and spectral analysis.

At the other extreme, to explore the synthetic potentiality of acetamide 2. Thus, coupling of acetamide 2 with diazonium salt derived from aniline furnished the hydrazonyl derivative 16 in good yield. Microanalysis and spectroscopic data of 16 were fully consistent with the proposed structure. Further investigations, phenylhydrazo-
nitrile derivative 16 contains three active centers, which attract to explore its utility to prepare new heterocyclic derivatives. Thus, treatment of 16 with ethyl cyanoacetate in boiling ethanol containing a few drops of piperidine gave the pyridazine derivative 17. Also, compound 16 was reacted with malononitrile in ethanol containing a few drops of triethylamine and gave the pyridine derivative 18, in good yield. Further elucidation of the structure of 16 came from the reaction with hydrazine hydrate in refluxing ethanol to furnish the pyrazole product 19. Finally, the reaction of 16 with hydroxylamine hydrochloride in refluxing dimethyl formamide containing sodium acetate produced the triazole derivative 20 (Scheme 2). All these structures were established based on elemental analysis and spectral data (see Experimental section).

3.2 Surface active agents

Nonionic surface active agents are very important for cleaning and industrial purposes as pharmaceutical synthesis, cosmetics, soaps and detergents due to their easy rinsing, good detergency and low foaming in the cleaning of milk and beer bottles. The surfactant producers and researchers have focused on how to synthesis new surfactants, which are biodegradable, lower in irritancy, manufactured and effective in their applications. Therefore, the aim of this work was to synthesis nonionic surface active agents incorporated heterocyclic moiety with an intermediate fatty chain to obtain higher biological and surface activity. Thus, the propoxylation of some the synthesized compounds (4-11, 13-15 and 17-20) by addition of 10 moles of propylene oxide in presence of KOH gave nonionic surface active agents (21-35) having a higher degree of antimicrobial and surface activity, which can be serve in the manufacture of drugs, cosmetic, antibacterial and antifungal compounds. This addition reaction is one of the principal processes used to introduce hydrophilic functional groups into a hydrophobic moiety and the reaction conditions are shown in Table 1. The structure of the products was confirmed based on IR and 1HNMR spectra (see Experimental section). The propoxylation of compounds 5, 6, 13 and 15 as representative examples are shown in Scheme 3.

3.3 Performance properties

In order to check the industrial feasibility for these compounds-based nonionic surfactants as replacements for petroleum and/or other commercial surfactants, performance properties as wetting ability, emulsion stability, and foaming were evaluated as shown in Table 2.

3.3.1 Surface tension

In an aqueous medium, the surfactant molecules are adsorbed at the air–water interface, where the hydrophilic part is directed to the water phase and the hydrophobic part is located at the air–water interface. The adsorption of surfactant molecules at the air–water interface decreases the surface tension of the solution as shown in Table 2. A marked decrease in the surface tension indicates that the

Scheme 2 Synthesis of pyrazole (13-15, 19), triazole 20, pyridine 18 and pyridazine 17 derivatives.
surfactant molecules have great tendency towards adsorption at the air–water interface. There is a significant reduction in the surface tension of water from 72 to 30–38 dynes/cm by using the prepared compounds. The results showed that, the surfactants 23, 24 and 28 have maximum ability while compound 21 has low aptitude to decrease the surface tension of aqueous system in the series of amphiphile. In addition, comparing structurally related surfactants 23, 25 and 28 indicated that, the thiophene derivatives 23, 28 are more effective in decreasing the surface tension than thiophene 25. In addition, the pyridine derivative 24 revealed high effective than pyridine derivatives 22, 33. Moreover, the pyrazole derivative 29 induce the highest reduction in surface tensions than other the related structure. Generally, the synthesized products have ability to decrease the surface tension, which indicated an increase in surface activity.

### 3.3.2 Interfacial tension

Interfacial tension is a property that determines the ability of compounds to locate at the interface between the oil and the water phase. The driving force of surfactant molecules to adsorb at the interface (boundary surfaces) is to decrease the free energy at these boundaries and this decrease was observed from the interfacial values. The tendency of surfactant molecules towards accumulation at the interfaces is unique property of surfactants. The interfacial tension values of the surfactants (21-35) were ranged between 8.0 and 11.5 mN/m at 25°C.

### 3.3.3 Cloud point

For nonionic surfactants, a common and characteristic observation is that they exhibit a reverse solubility versus temperature behavior in water, consequently their solutions are inclined to become evidently muddy at a well-defined temperature and this is called the cloud point, which the surfactant solution phase separates into two phases. The cloud point is an important factor for measuring the performance of nonionic surfactants. The measured values of cloud points for nonionic compounds were depicted in Table 2. The results showed that the synthesized compounds have high cloud points, which mean a good performance in hot water, and reflect the fact that it can be use over a wide range of temperatures. Generally, the nonionic surfactants showed optimal effectiveness when used near or below their cloud point. In addition, knowing the cloud point helps us to determine the storage stability because the storing at temperatures significantly higher than the cloud point may result in phase separation and instability.

### 3.3.4 Wetting ability

One of the major criteria for choosing a surfactant to be used in household or in industrial process is its wetting ability. For example, in laundry cleaning or textile processing use, the wetting power of surfactants may accelerate the diffusion or penetration of alkali chemicals and dyes into the fibers and improve the detergency or dyeing effects. Hence, we study the wetting properties of the synthesized surfactants as shown in Table 2. Among our products, the surfactants 23 and 24 exhibited the shortest sinking time, consequently, they have most efficient wetting agents among the studied groups. Generally, all of the surfactants showed good wetting ability.

### 3.3.5 Foaming Properties

The nonionic surfactants are useful in various applica-

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**Table 1**  Reaction conditions of propoxylated compounds.

| Sample | Temperature °C | Propoxylated products | Yield % | Color     | Shape   |
|--------|----------------|-----------------------|---------|-----------|---------|
| 4      | 110-120        | 21                    | 78      | Pale yellow | Semi-solid |
| 5      | 120-130        | 22                    | 85      | Brown     | Semi-solid |
| 6      | 130-140        | 23                    | 82      | Yellow brown | Solid |
| 7      | 110-120        | 24                    | 77      | Brown     | Semi-solid |
| 8      | 130-140        | 25                    | 86      | Pale yellow | Solid |
| 9      | 130-140        | 26                    | 79      | Yellow    | Solid |
| 10     | 135-145        | 27                    | 84      | Yellow brown | Solid |
| 11     | 125-135        | 28                    | 80      | Brown     | Semi-solid |
| 12     | 130-140        | 29                    | 75      | Brown     | Solid |
| 13     | 130-140        | 30                    | 80      | Pale yellow | Solid |
| 14     | 140-150        | 31                    | 86      | Pale yellow | Solid |
| 15     | 130-140        | 32                    | 88      | Pale yellow | Solid |
| 16     | 150–160        | 33                    | 78      | Brown     | Solid |
| 17     | 130-140        | 34                    | 76      | Pale yellow | Solid |
| 18     | 130-140        | 35                    | 80      | Brown     | Semi-solid |
tions that require a large or little amount of foam. For example, in washing hair, the foam from the shampoo not only surrounds the grease but also imparts a firm and fulfilling sensation; it would feel unpleasant if the foam were to disappear immediately. In the dyeing process, however, foams can be unwanted; they are created through passage of gas into the liquid during the motion of the machinery. If too much foam is present, contact between the dye solution and the fibers could be obstructed, resulting in uneven dyeing. As for the foaming properties of our synthetic products, their foam heights were ranged between 35 and 46 mm, which reveals that the products produced in this study exhibited foambilities properties.

3.3.6 Emulsion stability

Emulsion formation is an important property of the surfactants, which use in several applications, including foaming agents, paints, pharmaceutical, cosmetics, and food industries. In many textile processing operations, such as textile scouring and dyeing, the surfactants must be added in the dye bath to remove oil impurities from the fibers. During this process, the ability of the surfactants to emulsify the oil impurities is crucial. The emulsification ability of a surfactant was determined by the rate of diffusion of surfactant from bulk solution to the interface between oil and water and the physical properties of the adsorbed layers formed from surfactant molecules around

Scheme 3  Propoxylation of pyridine 5, thiophene 6, pyrazole (13, 15) derivatives.
the inner phase droplet. The results were summarized in Table 2, which showed that the synthesized surfactants have relatively low oil–water emulsion stability. The emulsions formed using the tested surfactants were ranged between 32 and 41 min. This shows the low emulsification tendency for these surfactants, and consequently their safe applicability in the field of petroleum applications including biocides and prevention of acidic dissolution of metals.

3.3.7 Biodegradability

For keeping the environment free from pollution, the biodegradability of the synthesized compounds was evaluated as shown in Table 3. The results of the biodegradation using surface tension measurements for 8 days, showed a gradual increase in the surface tension of the solutions by increasing time. The surface tension values of the solutions in the river water reached a maximum after 8 days and the gradual increase in the surface tension lead to the loss of the surface activity for the surfactant that dissolved in the river water. The loss of surface activity is may be due to the breaking of the molecules due to the biodegradation. The biodegradation products in the start of the test period (i.e., 1–4 days) have surface active character, which retains the surface activity of the solutions. At the end of the test period (5–8 days), the products lose their surface activity due to the severe degradation. The biodegradation values for these surfactants specifies them as biodegradable compounds and pass the international level (96% after 8 days), which means that these compounds are safe for human beings as well as for the environment.

### 3.4 Antimicrobial activity

The structure–activity studies showed that depending on the nature of the heterocyclic skeleton and its substituent, some of the newly synthesized compounds exhibit varying degree of microbial inhibition. The built up surfactant molecules containing heterocyclic moiety are most important class of surfactant active agents due to their dual characteristics, one due to conflict between the affinity of the hydrophobic and hydrophilic structure, which shows surface active properties and a second one that is due to the heterocyclic moiety confirmed with aid of a hydrophilic moiety (propylene oxide) give biological activity. It should be noted that, the studied compounds have the same hydrophobic (C18) and the hydrophilic structure (propylene oxide) but the difference in their structures for heterocyclic moiety as pyran, pyridines, thiophene, thiazole, pyrazoles, pyridazine and triazole derivatives which containing different function groups such as phenyl (Ph), nitrile (CN), carbonyl (CO), acetyl (COCH3), ester (COOEt) and /or thione (CS) groups, which caused a higher activity. Therefore, it can be deduced that the specific skeletons in their structures are responsible for the antibacterial and antifungal activities.

The results were depicted in Table 4, which revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive, Gram-negative bacterial and antifungal strains. It would be noticed that compounds belonging to the thiophene series (Scheme 1) exhibited better antibacterial potentials than the pyrazole, triazole and pyridine derivatives (Schemes 1).
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The results revealed that compounds 23, 28, and 32 exhibited broad spectrum antibacterial profile against Staphylococcus aureus (G+). Whereas, the Escherichia coli (G−) showed high responses for thiophene derivative 28. In addition, we noticed that, the pyridine 22 and thiazole 26 derivatives exposed moderate responses for Candida albicans. On the other hand, pyran 21, pyrazoles 29, 33 and pyridine 34 derivative exhibited weak to moderate...
ate growth inhibitory activity may be due to the azo group, which make a slight effect on the antibacterial activity. In conclusion, the nature of substituents and the heterocyclic skeleton of molecules have a strong influence on the extent of antibacterial and antifungal activities.

4 CONCLUSION

New classes of ecologically safe nonionic of surface active agents incorporated heterocyclic nucleus as pyran, thiophene, pyrazole, thiazole, triazole pyridine and pyridazine derivatives in different molecular weights were designed and synthesized in our laboratory from easily renewable and cheap resources. Propoxylation of these heterocycles with propylene oxide (10 moles) produced nonionic surfactants having surface active properties, which showed good degradation susceptibility within 8 days. The structure–activity studies showed that depending on the nature of heterocyclic skeleton and its substituents, the newly synthesized compounds exhibited varying degree of microbial inhibition. Therefore, it is clear that the tested surfactants can be used in the manufacture of dyes, drugs, cosmetics, emulsifiers, pesticides, luminophores for optical applications and many other industries with low toxicity to human beings and the environment owing to their solubility and good biodegradability. From this study, it is understandable that further derivatization and heterocyclization of these hetero-analogues from fatty compounds can be serve as new templates for antimicrobial drug discovery and could probably lead to more potent agents in this field.

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