Surface active properties and biological activity of novel nonionic surfactants containing pyrimidines and related nitrogen heterocyclic ring systems

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1. INTRODUCTION

In continuation of our syntheses of surface active agents containing a heterocyclic moiety (Amin et al., 2004; El-Sayed et al., 2005a; Amin et al., 2006; El-Sayed and El-Sayed, 2006; El-Sayed, 2006), it was interesting to prepare some biologically active heterocycles which constitute an important class of organic compounds with diverse biological activities. Numerous fatty alcohols are now more available in their pure form and inexpensive enough to provide the chemical field with a wealth of reactions in which fatty alcohols are used as raw material in a variety of industrial products like pharmaceuticals, cosmetics, surfactants, paints, etc. Pyrimidine nucleus is considered one of the most important classes of chemotherapeutic drugs especially among those which are used in large scale for the treatment of cancer and tumors (Xu et al., 2004), antiviral (Eman and Mohamed, 2004), antihistaminic (Maisa et al., 2004), analgesic activities (Aly and Nassar, 2004) and other pharmaceutical activities (Yvette and Aly, 2003)) in current medicinal use. In particular, our interest in developing an efficient syntheses of polyfunctionally substituted heterocycles using the readily obtainable pyrimidine as starting material from fatty alcohols motivated us to explore their potential use for the synthesis of polyfunctionally substituted pyrimidine derivatives useful for optimization of their biological activity. This encouraged us to continue our progress in applying octadecanol as starting material for synthesizing some new biologically active pyrimidine and fused pyrimidine derivatives. These compounds fulfill the following two requirements. First, an amphiphilic molecule must contain both a hydrophobic and a hydrophilic part. Second, the presence of active H-atoms, (NH, SH, OH and COOH) in the molecule which make the propyloxylation possible leading to the hydrophobic part in a desired hydrophilic-hydrophobic balance (Chaudhuri et al., 1987).
2. MATERIALS AND METHODS

Melting points are uncorrected. IR spectra in KBr were measured on a Pye-Uncam SP-1000 infrared spectrophotometer on a KBr disk or nujol. The $^1$HNMR spectra were obtained on a Varian EM-390-60 MHz spectrometer in (D$_2$) DMSO as the solvent, tetramethylsilane (TMS) served as an internal reference and chemical shifts are expressed as δ (ppm). Microanalyses were performed by the Micro analytical Unit at Cairo University. Antimicrobial and antifungal activity tests were carried out by the microbiology laboratory, Faculty of Science, Benha University, Egypt.

2.1. Chemical synthesis of heterocyclic derivatives

2.1.1. Synthesis of chlorooctadecane (2)

A mixture of octadecanol 1 (0.0095 mol), POCl$_3$ (0.29 mol) and PCl$_5$ (0.015 mol) was heated to reflux on a water bath for 4 h (Aly 2005). The mixture was poured gradually onto crushed ice and the separated product was filtered off and crystallized from benzene to give 2. Yield (1.52 g, 70%, yellow oil).

2.1.2. Synthesis of 4-octadecyloxybenzaldehyde (3)

Compound 2 (10 mmol) was added to a mixture of 4-hydroxybenzaldehyde (1.22 g, 10 mmol) and anhydrous K$_2$CO$_3$ (2.90g, 30 mmol) in dry acetone (50 ml). The mixture was heated to reflux on a water bath for 5-6 h, poured into ice-cold H$_2$O and then extracted with Et$_2$O. The Et$_2$O layer was dried (anh Na$_2$SO$_4$) and the solvent evaporated to give 3. Yield (1.52 g, 76% pale yellow solid), M.p. 186-88°. IR: 3420 (OH), 2920-2850 (CH aliphatic), 2228 (C=O), 1605 (C=N). 1HNMR (CDCl$_3$): 0.96 (t, 3H, Me), 1.22-1.35 (m, 32H, 16CH$_2$), 3.72 (t, 2H, CH$_2$-O), 9.71 (s, 1H, CHO) and 6.90-7.77 (m, 4H, ArH). Anal. calc for C$_{30}$H$_{45}$N$_3$O$_2$S: C 70.41, H 8.86, N 8.21, S 6.07%.

2.1.3. Synthesis of 6-(4-octadecyloxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-3-ylamine (8)

A mixture of 6 (0.06 mol) and hydrazine hydrate (2.3 ml) in BuOH was heated to reflux for 2 h. The resulting solid was collected by filtration and crystallized from BuOH to give 7. Yield (1.55 g, 78% red brown), M.p. 192-203°. IR: 3320-3180 (NH), 2850-2920 (CH aliphatic), 1605 (C=NC), 1HNMR (CDCl$_3$): 0.96 (t, 3H, Me), 1.28-1.35 (m, 32H, 16CH$_2$), 3.95 (t, 2H, CH$_2$-O), 6.92-7.78 (m, 4H, ArH) and 4.91 (bs, 4H, 2NH$_2$). Anal. calc for C$_{30}$H$_{45}$N$_3$O$_2$: C 70.39, H 8.69, N 19.16, found: C 70.28, H 8.67, N 19.16%.

2.1.4. Synthesis of 4-hydroxy-2-methylsulfanyl-6-(4-octadecyloxyphenyl)pyrimidine-5-carbonitrile (5)

A solution of 4 (0.01 mol) and Mel (0.01 mol) in ETOhNa (prepared by dissolving 1.0 g of Na in 50 ml of ETOh) was heated to reflux for 5 h. The mixture was then cooled and poured onto ice-cold H$_2$O. The solid produced after acidification with HCl was filtered off, washed with water and crystallized from ETOh to give 5. Yield (1.72 g, 85% brown solid), M.p. 126-28°. IR: 3420 (OH), 2920-2850 (CH aliphatic), 2218 (C=N), 1598 (C=NC). 1HNMR (CDCl$_3$): 0.95 (t, 3H, Me), 1.29-1.62 (m, 32H, 16CH$_3$) 2.53 (s, 3H, SCH$_3$), 3.94 (t, 2H, CH$_2$-O), 5.01 (s, 1H, OH) and 7.42-8.76 (m, 4H, ArH). Anal. calc for C$_{30}$H$_{45}$N$_3$O$_2$: C 70.41, H 8.86, N 8.21, S 6.31 %.

2.1.5. Synthesis of 4-chloro-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidine-5-carbonitrile (6)

A mixture of 5 (0.0095 mol), POCl$_3$ (0.29 mol) and PCl$_5$ (0.015 mol) was heated to reflux on a water bath for 4 h. The mixture was poured gradually onto crushed ice and the solid separated was filtered off and crystallized from benzene to give 6. Yield (1.32 g, 71% pale yellow crystal), M.p. 118-20°. IR: 3320-3180 (NHNH$_2$), 2915 and 2851 (CH aliphatic), 2220 (C=NC), 1610 (C=NC). 1HNMR (CDCl$_3$): 0.85 (t, 3H, Me), 1.25-1.52 (m, 32H, 16CH$_2$) 2.48 (s, 3H, SCH$_3$), 3.76 (t, 2H, CH$_2$-O) and 6.64-7.59 (m, 4H, ArH). Anal. calc for C$_{30}$H$_{44}$ClN$_3$S (521.78): C 70.41, H 8.82, N 8.26, S 6.31%.

2.1.6. Synthesis of 2,4-dihydrazino-6-(4-octadecyloxyphenyl)-pyrimidine-5-carbonitrile (7)

A mixture of 6 (0.06 mol) and hydrazine hydrate (2.3 ml) in BuOH was heated to reflux for 2 h. The resulting solid was collected by filtration and crystallized from BuOH to give 7. Yield (1.55 g, 78% red brown), M.p. 192-203°. IR: 3320-3180 (NH$_2$), 2920 and 2847 (CH aliphatic), 2228 (C=NC), 1605 (C=NC). 1HNMR (CDCl$_3$): 0.96 (t, 3H, Me), 1.28-1.35 (m, 32H, 16CH$_2$), 3.95 (t, 2H, CH$_2$-O), 6.92-7.78 (m, 4H, ArH) and 4.91 (bs, 4H, 2NH$_2$). Anal. calc for C$_{30}$H$_{44}$N$_3$O$_2$: C 70.39, H 8.69, N 19.16, found: C 68.29, H 8.82, N 19.24, S 6.31%.

2.1.7. Synthesis of 6-hydrazino-4-(4-octadecyloxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-3-ylamine (8)

A solution of 7 (0.001 mol) in BuOH (20 ml) was heated to reflux for 5 h. The solvent was removed at reduced pressure and the residue crystallized from BuOH to give 8. Yield (1.87 g, 88% yellow crystals),
M.p. 178-80°. IR: 3340-3200 (NH2 and NHNH2), 2913 and 2850 (CH aliphatic), 1598 (C=N). 1H NMR (DMSO): 0.96 (t, 3H, Me), 1.24-1.62 (m, 32H, 16CH2), 3.65 (t, 2H, CH2-O), 4.38 (brs, 2H, NH2), 5.22 (brs, 2H, NH2), 7.43-7.96 (m, 4H, ArH) and 8.12, 8.35 (2s, 2H, 2NH). Anal. calc for C29H47N7O5.22 (brs, 2H, NH2), 7.43-7.96 (m, 4H, ArH) and 3.04, 3.32 (d, 2H, CHCH2), 3.94 (t, 2H, CH2-O) and 6.90-7.72 (m, 4H, ArH). Anal. calc for C32H46N6OS2 (585.88): C 64.62, H 8.11, N 7.17, S 10.95, found C 65.60, H 8.09, N 7.17, S 10.95.

2.1.8. Synthesis of 4-mercapto-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidine-5-carbonitrile (9)

To a solution of 6 (0.01 mol) in ETOH (20 ml), thiourea (0.01 mol) was added and the reaction mixture was heated under reflux for 10 h. The solid obtained after cooling was crystallized from ETOH to give 9. Yield (1.05g, 59% pale yellow solid), M.p. 236-38°. IR: 3240 (NH2), 2913 and 2850 (CH aliphatic), 1670 (CO), 1610 (C=N), 1267 (CS). 1HNMR (CDCl3): 0.96 (t, 3H, Me), 1.29-1.62 (m, 32H, 16CH2), 2.48 (s, 3H, SCH3), 3.90 (t, 2H, CH2-O), 6.62-7.77 (m, 9H, ArH); 8.01 (s, 1H, NH). Anal. calc for C39H50N4O2S3 (703.05): C 66.63, H 7.17, N 7.97, S 13.68, found: C 66.60, H 7.15, N 7.91, S 13.73%.

2.1.11. Synthesis of 2-methylsulfanyl-4-(4-octadecyloxyphenyl)-7-phenyl-6-thioxo-6,7-dihydro-5H-9-thia-1,3,5,7-tetraaza-fluoren-8-one (12)

To a solution of 11 (0.001 mol) in pyridine (25 ml), phenyl isothiocyanate (0.001 mol) was added and the reaction mixture was refluxed in an oil bath for 20 h. The mixture after cooling was poured into ice/HCl and the solid separated was filtered, washed with cold ETOH, dried and crystallized from ETOH/DMF to give 12. Yield (1.05g, 59% pale yellow solid), M.p. 178-80°. IR: 3440 (OH), 2920, 2851 (CH aliphatic) and 1705, 1690 (CO of acid and ketone). 1HNMR (CDCl3): 0.96 (t, 3H, Me), 1.29-1.62 (m, 30H, 16CH2), 2.48 (s, 3H, SCH3), 3.90 (t, 2H, CH2-O), 6.62-7.77 (m, 9H, ArH); 8.01 (s, 1H, NH). Anal. calc for C39H50N4O2S3 (703.05): C 66.63, H 7.17, N 7.97, S 13.68, found: C 66.60, H 7.15, N 7.91, S 13.73%.

A mixture of 10 (0.01 mol) and thiosemicarbazide (0.01 mol) and POCl3 (0.01 mol) was warmed at 60° for 1 h and the temperature was raised to 90° for an additional 2h. The contents were poured onto crushed ice, cooled to 10°, pH adjusted to 10-12 M NaOH and the resulting solid was crystallized from DMF to give 13; yield (1.22g, 70% red brown crystals), M.p. 146-48°. IR: 3240 (NH), 2913 and 2850 (CH aliphatic), 1590 (C=N), 1267 (CS). 1HNMR (CDCl3): 0.80 (t, 3H, Me), 1.25-1.60 (m, 30H, 16CH2), 2.47 (s, 3H, SCH3), 3.45 (s, 2H, NH2), 3.80 (t, 2H, CH2-O) and 6.90-7.72 (m, 4H, ArH). Anal. calc for C32H46N6OS2 (594.89): C 64.61, H 7.79, N 14.13, S 10.78, found: C 64.65, H 7.77, N 14.18, S 10.81%.

2.1.12. Synthesis of 4-(5-amino-[1,3,4]thiadiazol-2-yl)-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidine-5-carbonitrile (13)

A solution of 9 (0.001 mol) and β-benzoylacrylic acid (0.002 mol) and chloroacetic acid (0.002 mol) in EIOH (30 ml) was heated under reflux for 3h. The precipitate formed after cooling was filtered and crystallized from benzene to yield 10. Yield (1.22g, 68% yellow crystals), M.p. 178-80°. IR: 3340-3200 (NH2 and NHNH2), 1725 (CO), 1610 (C=N). 1HNMR (DMSO): 0.96 (t, 3H, Me), 1.29-1.62 (m, 32H, 16CH2), 2.49 (s, 3H, SCH3), 3.90 (t, 2H, CH2-O), 6.91-7.76 (m, 4H, ArH) and 11.01 (s, 1H, OH). Anal. calc for C32H46N6OS2 (585.88): C 65.60, H 8.09, N 7.17, S 10.95, found C 65.62, H 8.11, N 7.20, S 10.98, %.

2.1.10. Synthesis of 5-amino-2-methylsulfanyl-4-(4-octadecyloxyphenyl)-thiophen2-carboxylic acid (11)

To a solution of 10 (0.01 mol) in EIOH (20 ml), EIONa (50 mg Na in 25 ml EIOH) was added by droplets and the mixture was heated under reflux for 30 min. The solid that formed while hot was collected and crystallized from EIOH to give 11. Yield (1.72g, 83% brown solid), M.p. 182-84°. IR: 3325, 3310 (NH2), 2918 and 2848 (CH aliphatic), 1725 (CO), 1610 (C=N). 1H NMR (CDCl3): 0.95 (t, 3H, Me), 1.22-1.60 (m, 32H, 16CH2), 2.50 (s, 3H, SCH3), 3.84 (t, 2H, CH2-O), 7.73-8.67 (m, 4H, ArH) and 4.80 (brs, 2H, NH2). Anal. calc for C32H46N6OS2 (585.88): C 65.60, H 8.09, N 7.17, S 10.95, found C 65.65, H 8.13, N 7.15, S 10.99%.
2.1.14. Synthesis of 2-methylsulfanyl-4-(4-octadecyloxyphenyl)-6-(3-oxo-6-phenyl-2,3,4,5-tetrahydropyrazidin-4-ylsulfanyl)-pyrimidine-5-carbonitrile (15)

A mixture of 14 (0.01 mol) and hydrazine hydrate (0.01 mol) in EIOH (40 ml) was heated under reflux for 5 h, then the solution was concentrated. The product was obtained by filtration and crystallized from EIOH to give 15. Yield (1.65 g, 78% red brown solid), M.p. 190-92°C. IR: 3370 (NH), 2919 and 2854 (CH aliphatic), 2225 (C=O) from EtOH to give 16. Yield (1.43g, 65% pale yellow crystals), M.p. 185-187°C. IR: 2919 and 2851 (CH aliphatic), 2225 (C=O) and 1680 attributed to carbonyl of cyclic ether. 1H NMR (CDCl3): 0.96 (t, 3 H, Me), 1.25-1.60 (m, 32 H, 16CH2), 2.35, 2.60 (d, 2H, CHCH2CH of oxazin ring), 3.52 (t, 1H, CHCH2 of pyridazine ring), 3.80 (t, 3 H, Me), 1.29-1.62 (m, 32 H, 16CH2), 1.87, 2.21 (d, 2H, CHCH2 of pyridazine ring), 2.47 (s, 3H, SCH3), 3.41 ( t, 1H, CHCH2 of oxazin ring), 8.01 ( s, 1 H, NH) and 6.81-7.25 ( m, 9H, ArH). Anal. calc for C40H53N5O2S2 (700.03): C 68.62, H 7.50, N 10.00, S 9.17 %. Found: C 68.63, H 7.63, N 10.00, S 9.16 %.

2.1.15. Synthesis of 2-methylsulfanyl-4-(4-octadecyloxyphenyl)-6-(6-oxo-3-phenyl-5,6-dihydro-2H-[1,2]oxazin-5-ylsulfanyl)-pyrimidine-5-carbonitrile (16)

A mixture of 14 (0.01 mol) and NH2OH/HCl (0.01 mol) in pyridine (20 ml) and a few drops of H2O was heated under reflux for 12 h. The mixture was poured onto ice-cold HCl. The product was obtained by filtration and crystallized from EIOH to give 16. Yield (1.43g, 65% pale yellow crystals), M.p. 185-187°C. IR: 2919 and 2851 (CH aliphatic), 2225 (C=O) and 1680 attributed to carbonyl of cyclic ether. 1H NMR (CDCl3): 0.96 (t, 3 H, Me), 1.25-1.60 (m, 32 H, 16CH2), 2.35, 2.60 (d, 2H, CHCH2CH of oxazin ring), 2.51 (s, 3H, SCHO), 3.41 (t, 1H, CHCH2 of oxazin ring), 3.81 (t, 1H, CHCH2 of oxazin ring), 8.01 (s, 1 H, NH) and 6.81-7.25 ( m, 9H, ArH). Anal. calc for C40H53N5O2S2 (701.01): C 68.54, H 7.48, N 7.99, S 9.15, found C 68.58, H 7.50, N 7.96, S 9.17 %.

2.2. Conversion of the prepared compounds to nonionic surfactants

Nonionic surfactants are prepared by the addition of n moles of propylene oxide (n = 5, 10, 15) to one mol of suitable product using KOH as catalyst. A complete description of the procedure is given in (Morgos et al., 1983a). The addition of propylene oxide gave a mixture of propoxylated products whose structures were confirmed by IR and 1H NMR spectra. IR spectra showed two broad bands at 1100 and 950 cm⁻¹ characteristic for vC-O-C ether linkage of polypropenoxy chain and 1H NMR spectra showed the protons of propoxyl groups δ = 3.2-3.7 (m, -CH2CH(CH3)-O)-.

2.3. Determination of the performance properties

2.3.1. Surface and interfacial tension were measured with a Du-Nouy tensiometer (Findly, 1963) (Kruss, Type 8451) using an aqueous solution of surfactants (0.1 wt %) at room temperature (25°C).

2.3.2. Cloud point was determined by gradually heating a surfactant solution (1.0 wt %) in a bath of controlled temperature, and recording the temperature at which the clear, or nearly clear solutions become definitely turbid. The reproducibility of this temperature was checked by cooling the solutions until they become clear again (Wiel et al., 1963).

2.3.3. Wetting time was determined by immersing a sample of cotton fabric in 1.0 wt % aqueous solution of surfactants (Draves and Clarkso, 1931).

2.3.4. Foaming properties were measured according to (El-Sukkary et al., 1987). In this procedure a 25 ml solution (1.0 wt %) was shaken vigorously for 10 seconds in a 100 ml graduated cylinder with a glass stopper at 25°C. The solution was allowed to stand for 30 seconds and then the foam height was measured.

2.3.5. Emulsification stability was prepared from 10 ml of a 20 mmol aqueous solution of surfactant and 5 ml of toluene at 40°C. Emulsion stability was determined as the time which 9 ml of aqueous layer took to separate from the emulsion counting since cession of shaking (Takehski, 1970).

2.4. Biodegradability

Biodegradability was evaluated by surface tension measurements which were taken each day, on each sample during the degradation test. Biodegradation percent (D) (Eter et al., 1974) for each sample was calculated using the following equation: D = [(γ - γ0) / (γ - γ0)] x 100, where γ = surface tension at time t, γ0 = surface tension at zero time, γ0 = surface tension of blank experiment at time t (without sample).

2.5. Biological activity

The biological activities of these compounds have been evaluated by filter paper disc method (Rosen, 1989). After dissolving in N,N-dimethylformamide to obtain a 1mg/mL solution (1000 ppm). The inhibition zones of incubation period of 3 days at 37°C for Echerichia coli and 28°C for other bacteria and fungi were recorded. N, N-Dimethylformamide alone showed no inhibition zone.

3. RESULTS AND DISCUSSION

3.1. Synthesis

The reaction of octadecanol (1) with POCl3/PCl5 gave 1-chlorooctadecane (2) (Wanchai Warinthorn,
2006) which was heated to reflux with 4-hydroxybenzaldehyde in dry acetone in the presence of anhydrous K$_2$CO$_3$ (Gean et al., 2001) to produce 4-octadecyloxybenzaldehyde (3). The latter was allowed to condense with ethyl cyanoacetate and thiourea to afford 6-(4-octadecyloxy-phenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4) according to Scheme 1.

Pyrimidine derivative 4 was used in the synthesis of alkylsulfanylpyrimidine derivatives that have recently been identified as highly specific reverse transcriptase inhibitors against human immunodeficiency virus. Thus, the reaction of 4 with Mel in the presence of EtONa afforded 4-hydroxy-2-methylsulfanyl-6-(4-octadecyloxyphenyl)pyrimidine-5-carbonitrile (5) and treatment of 5 with POCl$_3$/PCl$_5$ on a water bath yields 4-chloro-2-methylsulfanyl-6-(4-octadecyloxyphenyl)pyrimidine-5-carbonitrile (6).

The electron deficient nature of the pyrimidine ring of 6 and the high reactivity of the methylthio group towards nucleophile reagents facilitated the synthesis of a large number of condensed pyrimidines via nucleophilic aromatic substitutions. Thus, the reaction of 6 with hydrazine in refluxing BuOH for 2h gave 2,4-dihydrazino-6-(4-octadecyloxyphenyl)pyrimidine-5-carbonitrile (7), which was further cyclized to 6-hydrazino-4-(4-octadecyloxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-3-ylamine (8) by refluxing in BuOH for 5 h.

The formation of 8 occurs via nucleophilic attack of the hydrazino moiety to the CN group in ortho position. Treatment of 6 with thiourea in EtOH solution produced 4-mercaptop-2-methylsulfanyl-6-(4-octadecyloxyphenyl)pyrimidine-5-carbonitrile (9). Alkylation of 9 with chloroacetic acid in EtOH solution containing AcONa afforded S-alkylated derivative 10 that was cyclized to thienopyrimidine derivative 11 in EtOH containing EtONa.

Of particular interest is a cyclocondensation reaction of thienopyrimidine 11 with phenyl isothiocyanate which resulted in the formation of the tricyclic heterocycle 12.

In the present investigation, compound 10 was used to add an aminothiadiazole moiety to the pyrimidine system via the condensation with thiosemicarbazide in presence of POCl$_3$, it underwent ring closure to give aminothiadiazole derivative 13. Furthermore, the reaction of 9 with [1-benzoylacrylic acid in dry benzene and in the presence of a few drops of piperidine gave 2-[5-cyano-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidin-4-ylsulfanyl]-4-oxo-phenyl-butyric acid (14), which was used to construct another heterocyclic nucleus of biological interest. Thus, the reaction of 14 with hydrazine hydrate in boiling EtOH afforded 2-methylsulfanyl-4-(4-octadecyloxyphenyl)-6-(3-oxo-6-phenyl-2,3,4,5-tetrahydropyridazin-4-ylsulfanyl)-pyrimidine-5-carbonitrile (15). Condensation of 14 with hydroxylamine hydrochloride in boiling pyridine yielded 2-methylsulfanyl-4-(4-octadecyloxy-phenyl)-6-(6-oxo-3-phenyl-5,6-dihydro-2H-[1,2] oxazin-5-ylsulfanyl)-pyrimidine-5-carbonitrile (16) (Scheme 2).

### Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conversion</th>
<th>Surface and interfacial tension</th>
<th>foaming</th>
<th>Good detergency</th>
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<td>4</td>
<td>17a-c</td>
<td>28a-c</td>
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3.2. Conversion of the prepared compounds (4-16) to nonionic surfactants (17a-c to 28a-c)

Propylene oxide condensation is one of the principal processes employed to introduce a hydrophilic functional group into organic compounds. The ultimate objective of the process is the production of surface active agents having the desired hydrophilphilic balance for such commercial applications such as detergents, emulsification, wetting and textile processing (Ahmed, 2004). One of the most important groups of surfactants with growing industrial interest is the nonionic, which can be synthesized by propoxylation with the propylene oxide of compounds, which contain XH groups in the presence of KOH as a catalyst, as the following equation

\[ R\cdot XH + n\ H_2C\cdot C\cdot Me \xrightarrow{\text{catalyst}} RX(CH_2\cdot CH_2\cdot O)_nH \]

R is a long chain aliphatic hydrocarbon (C$_{18}$), XH is OH, SH, COOH, NH, NH$_2$ and (n) the moles of propylene oxide (n = 5, 10, 15 mole) reacted with one mole of starting molecules. The addition of propylene oxide gave nonionic surfactants (17a-c to 28a-c). The reaction conditions are illustrated in Table 1. Scheme 3 shows the propoxylation of compounds 4 and 11 as an example.

### 3.3. Surface active properties

Nonionic surfactants find diverse applications, both in industry and in the home. Their moderate foaming and good detergent are employed in a variety of ways in the leather industry, accelerated soaking and liming are improved by the addition of wetting agents (El-Dougdoug and Ahmed, 2004). The study of the surface active properties of the oxypropylated compounds has been done in an aqueous solution (1wt %, pH = 7) at 25°C. The surface activity and related properties of the synthesized compounds including surface and interfacial tension, cloud point, wetting time, foaming and emulsification properties are given in Table 2.

#### 3.3.1. Surface and interfacial tension

The surface and interfacial tension of the prepared compounds are shown in Table 2. It can be observed that the alkyl chain length gives rise to increased hydrophobic interaction between the alkyl chains and also to increased hydrophobic hydration effects that in turn may reduce the surface tension which provide these compounds with pronounced surface activity.

#### 3.3.2. Cloud point

A very important factor in making the most efficient use of nonionic surfactants in an aqueous

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**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Surface and interfacial tension</th>
<th>Foaming</th>
<th>Good detergency</th>
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<td>11</td>
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SURFACE ACTIVE PROPERTIES AND BIOLOGICAL ACTIVITY OF NOVEL NONIONIC SURFACTANTS CONTAINING PYRIMIDINES...

**Scheme I**
Reagents: (i) POCl₃/PCl₅; (ii) HOCl₂H₂CHO[p]; (iii) K₂CO₃; (iv) acetone; (v) NCCH₂COOC₂H₅; (vi) NH₂CSNH₂; (vii) EtOH

**Scheme II**
Reagents: (i) Mel; (ii) POCl₃/PCl₅; (iii) NH₃NH₂; (iv) BuOH; (v) NH₂CSNH₂; (vi) CICH₂COOH, (vii) AcONa; (viii) EtONa; (ix) PhNCS; (x) NH₂NHCNSNH₂; (xi) POCl₃; (xii) PhCOCH=CH-COOH; (xiii) NH₂OH.HCl
### Table 1

**Reaction conditions of propenoxylated compounds**

<table>
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<tr>
<th>Compd</th>
<th>Catalyst, wt %</th>
<th>Temperature °C</th>
<th>Propoxylated Product</th>
<th>Yield %</th>
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<tr>
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* n* Degree of propenoxylation was calculated by weight.

### Table 2

**Surface properties of nonionic compounds a**

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<th>Interfacial Tension (dyne/cm) 0.1 %</th>
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<th>Wetting time (sec.) 1%</th>
<th>Emulsion stability (min. sec) 1%</th>
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* Error was: Surface and interfacial tensions = ± 0.1 dynes/cm; Cloud point = ± 1 °C; foam height = ± 2 mm; Wetting time = ± 1 sec; emulsion = ± 1 min.

b n in the number of propylene oxide added to the chosen compound.
system is an understanding of the property called cloud point. All these compounds showed high cloud points which gave performance in hot water and it was increased by increasing the number of the propoxy group.

3.3.3. Wetting time

All the prepared compounds showed a decrease in wetting time with an increase in the number of propylene oxide units in the molecule. Moreover, the presence of propylene oxide in different moles caused a reduction in wetting time, i.e. improving their wetting properties which make widely applicable in the textile industry (Somaya et al., 1998).

3.3.4. Foam properties

Nonionic surfactants containing an aromatic ring such showed poor foaming properties. The foam height of the prepared surfactants increases with an increase in the number of propylene oxide units per molecule of surfactant. The low foaming power could have an application in the dyeing auxiliary industry (Morgos et al., 1983b).

3.3.5. Emulsion stability

Emulsification is one of the most important properties of surfactants. In many textile processes such as scouring and dyeing, it is necessary to introduce surfactants into the bath to remove oily impurities from the fibers. On the other hand, nonionic surfactants with good emulsion stability have been used in such fields as, shampoos, cosmetics, emulsion paints and the textile industry. The results in Table 2 showed that the emulsion stability increases by decreasing the number of propylene oxide units.

3.4. Biodegradability

The trend of degradation in river die-away tests was followed by surface tension measurements. The results are given in Table 3. The rate of degradation of these compounds depends on the size of the molecule; a bulky molecule diffuses through the cell membrane, and its degradation is more difficult. This means that molecules with a low proportion of propylene oxide are more easily degraded than those containing a higher proportion.

3.5. Biological activity

All the prepared compounds were screened for their activity against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis, Bacillus cereus), Gram-negative bacteria (Pseudomonas aurignosa, Echerichia coli, Enterobacter aerogenes), as well as fungi (Aspergillus niger, Penicillium italicum, Fusarium oxysporum). Also, a comparison between the activity of our synthesized compounds and sulphadiazine as standard drug was discussed. The results are listed in Tables 4 and 5. It is apparent from Table 4 that some of the synthesized compounds showed antibacterial activity.

However, concerning the activity against Gram-positive bacteria (Bacillus subtilis), compounds 21c, 26c, 27c and 28c showed excellent activity,
compounds 22b, 23c, 24c and 25c exhibit good activity, whereas compounds 17a, 18a, 18c and 19c showed moderate activity. On the other hand, the Gram-negative bacteria (Pseudomonas aurignosa) showed high responses to five of the prepared products. Compound 28c exhibits excellent antibacterial activity towards Enterobacter aerogenes.

Concerning the data of antifungal activity in Table 5, compounds 21b and 25b showed excellent activity against Aspergillus niger, while compounds 23b, 24b, 25c and 26c exhibit good activity. Also, compound 28b displays good activity toward Penicillium italicum. In general, the data obtained from the microbiological screening showed that the activity of most of the synthesized compounds showed moderate activity.

4. CONCLUSION

It can be concluded that all prepared nonionic surfactants exhibited antibacterial and antifungal properties as well as emulsifier properties. Therefore, their potential use in a non edible media such as insecticides or pesticides as well as in the manufacturing of drugs, cosmetics, antibacterial and/or antifungal is recommended.

ACKNOWLEDGMENTS

Origin of cultures: Botany Department, Faculty of Science, Benha University, Egypt.

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El-Sayed R. 2006. Synthesis, antibacterial and surface activity of 1,2,4-triazole derivatives. *Grasas Aceites.* **57** (2) 180-188.


Table 4

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* Sulphadiazine + + + + + + + + + + + + + + + +

* Error of calculations was: Biodegradation rate = ± 0.5 %.
Table 5
Antifungal activity of the prepared compounds

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