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

By **R. El-Sayed**

Chemistry Department, Faculty of Science, Benha University, Egypt.
E-mail: ref_at@hotmail.com

RESUMEN

Propiedades tensoactivas y actividad biológica de nuevos surfactantes no iónicos conteniendo pirimidinas y anillos nitrogenados relacionados.

Una serie de derivados pirimidínicos y relacionados han sido preparados vía diferentes reacciones de formación de heterociclos entre 6-(4-octadeciloxifenil)-4-oxo-2-tioxo-1,2,3,4-tetrahidropirimidina-5-carbonitrilo (4) y diferentes electrófilos y nucleófilos. Estos heterociclos tienen un átomo de hidrógeno activo (NH, OH, o COOH) que fue propoxilado con diferentes moles de óxido de propileno (5, 10, o 15) para producir surfactantes no iónicos con una cadena alquílica larga y peso molecular apropiado para convertirse en una molécula anfifílica con un balance hidrofílico-lipofílico correcto que aumenta la solubilidad y la biodedradabilidad, decrece la toxicidad a los seres humanos, y se convierte en respetuoso con el medio ambiente. Además, las actividades antimicrobianas de estos compuestos fueron determinadas y se encontró que algunos de estos compuestos tuvieron una actividad similar o más alta que antibióticos comerciales (sulfadiazina), lo que los hace apropiados para aplicaciones diversas como la manufactura de medicamentos, pesticidas, emulsificantes, cosméticos, etc.

PALABRAS-CLAVE: *Síntesis – Propiedades tensoactivas – Actividad antimicrobiana*

SUMMARY

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

A series of annelated pyrimidine derivatives has been synthesized via different heterocyclization reactions of suitably functionalized 6-(4-octadecyloxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4) with different electrophiles and nucleophiles. These heterocycles bear an active hydrogen atom (NH, OH or COOH) which could be propoxylated using propylene oxide with different moles, 5, 10 and 15, to produce nonionic surfactant having a long alkyl chain with molecular weight suitable for becoming an amphiphilic molecule with correct hydrophilic-lypophilic balance which enhances solubility, biodegradability and hence lowers the toxicity to human beings and becomes environmentally friendly. In addition, the antimicrobial activities of these compounds were screened and it was found that some of these compounds have similar or higher activity compared with commercial antibiotic drugs (sulphadiazine), which make them suitable for diverse applications like the manufacturing of drugs, pesticides, emulsifiers, cosmetics, etc.

KEY-WORDS: *Antimicrobial activity – Surface activity – Synthesis.*

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; Eissa 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 resence 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 (Chaudlhuri *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_6) DMSO as the solvent, tetramethylsilane (TMS) served as an internal reference and chemical shifts are expressed as δ (ppm). Microanalyses were preformed 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_2CO_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_2O and then extracted with Et_2O. The Et_2O layer was dried (anh Na_2SO_4) and the solvent evaporated to give 3. Yield (1.52g, 76% pale yellow solid), M.p. 126-28°. IR: 2913 and 2850 (CH aliphatic), 1695 (C=O), 820 and 690 (C–O). ^{1}HNMR ($CDCl_3$): 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 $C_{25}H_{42}O_2$ (374.61): C 80.16, H 11.30, found: C 80.20, H 11.32 %.

2.1.3. Synthesis of 6-(4-octadecyloxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4)

A mixture of 4-octadecyloxybenzaldehyde (3) (0.01 mol), ethyl cyanoacetate (0.01 mol), thiourea (0.01 mol) and K_2CO_3 (0.01 mol) in EtOH (40 ml) was heated to reflux for 24h. The precipitate formed after cooling and acidification was filtered off and crystallized from DMF/H_2O to give 4. Yield (0.82 g, 52% red brown crystals), M.p. 118-20°. IR: 3220-3180 (NH), 2950-2820 (CH aliphatic), 2225 (C≡N), 1675 (CO), 1600 (C=N), 1260 (CS). ^{1}HNMR (DMSO) δ: 0.90 (*t*, 3H, Me), 1.29-1.32 (*m*, 32H, $16CH_2$), 3.84 (*t*, 2H, CH_2-O), 6.70-7.76 (*m*, 4H, ArH) and 8.22 (*brs*, 2H, 2NH). Anal. calc for $C_{29}H_{43}N_3O_2S$ (497.75): C 69.98, H 8.71, N 8.44, S 6.44, found: C 69.95, H 8.72, N 8.47, S 6.49 %.

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

A solution of 4 (0.01 mol) and MeI (0.01 mol) in EtONa (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_2O. The solid product obtained 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. 186-88°. IR: 3420 (OH), 2920-2850 (CH aliphatic), 2218 (C≡N), 1598 (C=N). ^{1}HNMR ($CDCl_3$): 0.95 (*t*, 3H, Me), 1.29-1.62 (*m*, 32H, $16CH_2$) 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 $C_{30}H_{45}N_3O_2S$ (511.78): C 70.41, H 8.86, N 8.21, S 6.27,found: C 70.40, H 8.82, N 8.26, 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. 167-69°. IR: 2915 and 2851 (CH aliphatic), 2220 (C≡N), 1610 (C=N). ^{1}HNMR ($CDCl_3$): 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 $C_{30}H_{44}ClN_3OS$ (530.22): C 67.96, H 8.36, N 7.93, Cl 6.69, S 6.05,found: C 67.95, H 8.33, N 7.97, Cl 6.70, S 6.07%.

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. 192-93°. IR: 3320-3180 ($NHNH_2$), 2920 and 2847 (CH aliphatic), 2228 (C?N), 1605 (C=N). ^{1}HNMR ($CDCl_3$): 0.96 (*t*, 3H, Me), 1.29-1.32 (*m*, 32H, $16CH_2$), 3.95 (*t*, 2H, CH_2-O), 4.91, 4.96 (*brs*, 4H, $2NH_2$), 6.92-7.78 (*m*, 4H, ArH) and 8.11, 8.13 (*2s*, 2H, 2NH). Anal. calc for $C_{29}H_{47}N_7O$ (509.38): C 68.33, H 9.29, N 19.24, found: C 68.29, H 9.29, N 19.22%.

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 (1.87g, 88% yellow crystals),

M.p. 178-80°. IR: 3340-3200 (NH_2 and $NHNH_2$), 2913 and 2850 (CH aliphatic), 1598 (C=N). ^{1}H NMR (DMSO): 0.96 (*t*, 3H, Me), 1.24-1.62 (*m*, 32H, $16CH_2$), 3.65 (*t*, 2H, CH_2-O), 4.38 (*brs*, 2H, NH_2), 5.22 (*brs*, 2H, NH_2), 7.43-7.96 (*m*, 4H, ArH) and 8.12, 8.35 (*2s*, 2H, 2NH). Anal. calc for $C_{29}H_{47}N_7O$ (509.74): C 68.33, H 9.29, N 19.24,found: C 68.30, H 9.25, N 19.20%.

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 (1.82g, 81% white yellow solid), M.p. 156-58. IR: 2918 and 2845 (CH aliphatic), 2330 (SH), 2227 (C≡N), 1600 (C=N). ^{1}HNMR ($CDCl_3$): 0.90 (*t*, 3H, Me), 1.28-1.60 (*m*, 32H, $16CH_2$), 2.48 (*s*, 3H, SCH_3), 3.53 (*s*, 1H, SH), 3.94 (*t*, 2H, CH_2-O) and 6.64-7.46 (*m*, 4H, ArH). Anal.calc for $C_{30}H_{45}N_3S_2O$ (527.84): C68.26, H 8.59, N 7.96, S 7.95; found: C 68.30, H 8.62, N 7.95, S 7.99%.

2.1.9. Synthesis of [5-cyano-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidin-4-ylsulfanyl]-acetic acid (10)

A mixture of 9 (0.001 mol), AcONa (0.003 mol) and chloroacetic acid (0.001 mol) in EtOH (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. 195-96°. IR: 2921 and 2851 (CH aliphatic), 2218 (C≡N), 1720 (CO), 1610 (C=N). ^{1}HNMR (DMSO): 0.95 (*t*, 3H, Me), 1.29-1.62 (*m*, 32H, $16CH_2$), 2.49 (*s*, 3H, SCH_3), 3.90 (*t*, 2H, CH_2-O), 3.85 (*s*, 2H, SCH_2), 6.91-7.76 (*m*, 4H, ArH) and 11.01 (*s*, 1H, OH). Anal. calc for $C_{32}H_{47}N_3O_3S_2$ (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)-thieno[2,3-d]pyrimidine-6-carboxylic acid (11)

To a solution of 10 (0.01 mol) in EtOH (20 ml), EtONa (50 mg Na in 25 ml EtOH) 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 EtOH to give 11. Yield (1.72g, 83% brown solid), M.p. 182-84°. IR: 3325, 3310 (NH_2), 2918 and 2848 (CH aliphatic), 1725 (CO), 1610 (C=N). ^{1}H NMR ($CDCl_3$): 0.95 (*t*, 3H, Me), 1.22-1.60 (*m*, 32H, $16CH_2$), 2.50 (*s*, 3H, SCH_3), 3.84 (*t*, 2H, CH_2-O), 7.73-8.67 (*m*, 4H, ArH) and 4.80 (*brs*, 2H, NH_2). Anal. calc for $C_{32}H_{47}N_3O_3S_2$ (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%.

2.1.11. 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. 236-38°. IR: 3240 (NH), 2913 and 2850 (CH aliphatic), 1670 (CO), 1610 (C=N), 1267(CS). ^{1}HNMR ($CDCl_3$): 0.96 (*t*, 3H, Me), 1.29-1.62 (*m*, 32H, $16CH_2$), 2.48 (*s*, 3H, SCH_3), 3.90 (*t*, 2H, CH_2-O), 6.62-7.77 (*m*, 9H, ArH); 8.01 (*s*, 1H, NH). Anal. calc for $C_{39}H_{50}N_4O_2S_3$ (703.05): C 66.63, H 7.17, N 7.97, S 13.68, found: C 66.60, H 7.15, N 8.01, S 13.73%.

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

A mixture of 10 (0.01 mol) and thiosemicarbazide (0.01 mol) and $POCl_3$ (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 8-10 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_2), 2918 and 2852 (CH aliphatic), 2225 (C≡N) and 1590 (C=N). ^{1}HNMR ($CDCl_3$): 0.80 (*t*, 3H, Me), 1.25-1.60 (*m*, 30 H, $16CH_2$), 2.47 (*s*, 3H, SCH_3), 3.45 (*s*, 2 H, NH_2), 3.80 (*t*, 2H, CH_2-O) and 6.90-7.72 (*m*, 4H, ArH). Anal. calc for $C_{32}H_{46}N_6OS_2$ (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%.

2.1.13. Synthesis of 2-[5-cyano-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidin-4-ylsulfanyl]-4-oxo-4-phenyl-butyric acid (14)

A solution of 9 (0.002 mol) and β-benzoylacrylic acid (0.002 mol) and a few drops of pyridine in dry benzene (50 ml) was left at room temperature for 48 h (El-Sayed *et al.*, 2005b). The mixture was concentrated under reduced pressure and the cold mixture was washed with light petroleum ether. The solid obtained was crystallized from benzene to give 14; yield (1.72g, 85% brown solid), M.p. 226-28°. IR: 3440 (OH), 2920, 2851 (CH aliphatic) and 1705, 1690 (CO of acid and ketone). ^{1}HNMR ($CDCl_3$): 0.95 (*t*, 3 H, Me), 1.29-1.62 (*m*, 32 H, $16CH_2$), 2.47 (*s*, 3H, SCH_3), 3.92 (*t*, 1H, $CHCH_2$), 3.04, 3.32 (*d*, 2H, $CHCH_2$), 3.94 (*t*, 2H, CH_2-O), 7.35-7.91 (*m*, 9H, ArH) and 11.01 (*s*, 1 H, OH). Anal. calc for $C_{40}H_{53}N_3O_4S_2$ (704.01): C 68.24, H 7.59, N 5.97, S 9.11, found: C 68.27, H 7.63, N 5.95, S 9.15%.

2.1.14. Synthesis of 2-methylsulfanyl-4-(4-octadecyloxyphenyl)-6-(3-oxo-6-phenyl-2,3,4,5-tetrahydropyridazin-4-ylsulfanyl)-pyrimidine-5-carbonitrile (15)

A mixture of 14 (0.01 mol) and hydrazine hydrate (0.01 mol) in EtOH (40 ml) was heated under reflux for 5 h, then the solution was concentrated. The product was obtained by filtration and crystallized from EtOH to give 15. Yield (1.65 g, 78% red brown solid), M.p. 190-92°. IR: 3370 (NH), 2919 and 2850 (CH aliphatic), 2220 (C≡N), 1675 (CO of pyridazine), and 1590 (C=N). ^{1}HNMR ($CDCl_3$): 0.95 (*t*, 3 H, Me), 1.29-1.62 (*m*, 32 H, $16CH_2$), 1.87, 2.21 (*d*, 2H, $CHCH_2$ of pyridazine ring), 2.47 (*s*, 3H, SCH_3), 3.52 (*t*, 1H, $CHCH_2$ of pyridazine ring), 3.80 (*t*, 2H, CH_2-O), 7.02 (*s*, 1 H, NH) and 7.30-7.71 (*m*, 9H, ArH). Anal. calc for $C_{40}H_{53}N_5O_2S_2$ (700.03): C 68.63, H 7.63, N 10.00, S 9.16, found C 68.62, H 7.60, N 10.06, S 9.19%.

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 NH_2OH/HCl (0.01 mol) in pyridine (20 ml) and a few drops of H_2O was heated under reflux for 12 h. The mixture was poured onto ice-cold HCl. The product was obtained by filtration and crystallized from EtOH to give 16. Yield (1.43g, 65% pale yellow crystals), M.p. 185-87°. IR: 2919 and 2851 (CH aliphatic), 2225 (C≡N) and 1680 attributed to carbonyl of cyclic ether.^{1}H NMR ($CDCl_3$): 0.96 (*t*, 3 H, Me), 1.25-1.60 (*m*, 32 H, $16CH_2$), 2.35, 2.60 (*d*, 2H, $CHCH_2CH$ of oxazin ring), 2.51 (*s*, 3H, SCH_3), 3.41 (*t*, 1H, $CHCH_2$ of oxazin ring), 3.81 (*t*, 1H, CH_2CH of oxazin ring), 8.01 (*s*, 1 H, NH) and 6.81-7.25 (*m*, 9H, ArH). Anal. calc for $C_{40}H_{52}N_4O_3S_2$ (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 propenoxylated products whose structures were confirmed by IR and ^{1}HNMR spectra. IR spectra showed two broad bands at 1100 and 950 cm^{-1} characteristic for νC-O-C ether linkage of polypropenoxy chain and ^{1}HNMR spectra showed the protons of propenoxy groups δ = 3.2-3.7 (m, $-CH_2CH(CH_3)$-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°. 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°. Emulsion stability was determined as the time which 9 ml of aqueous layer took to separate from the emulsion counting since cession of shaking (Takeshi, 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: $D = [(\gamma_t - \gamma_o) / (\gamma_{bt} - \gamma_o)] \times 100$, where γ_t = surface tension at time t, γ_o= surface tension at zero time, γ_{bt}= 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° for Echerichia coli and 28° 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 $POCl_3$/PCl_5 gave 1-chlorooctadecane (2) (Wanchai Warinthorn,

2006) which was heated to reflux with 4-hydroxybenzaldehyde in dry acetone in the presence of anhydrous K_2CO_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 MeI 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 nucleophilic reagents facilitated the synthesis of a large number of condensed pyrimidine *via* nucleophilic aromatic substitutions. Thus, the reaction of 6 with hydrazine hydrate 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)-1*H*-pyrazolo[3,4-d]pyrimidin-3-ylamine (8) by refluxing in BuOH for 5 h.

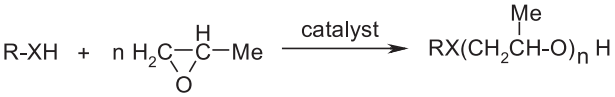
The formation of 8 occurs *via* nucleophilic attack of the hydrazino moiety to the CN group in *ortho* position. Treatment of 6 with thiourea in EtOH solution produced 4-mercapto-2-methylsulfanyl-6-(4-octadecyloxyphenyl)-pyrimidine-5-carbonitrile (9). Alkylation of 9 with chloroacetic acid in EtOH solution 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 β-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-4-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-2*H*-[1,2] oxazin-5-ylsulfanyl)-pyrimidine-5-carbonitrile (16) (Scheme 2).

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 hydrophile-lipophile 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 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 propenoxylation of compounds 4 and 11 as an example.

3.3. Surface active properties

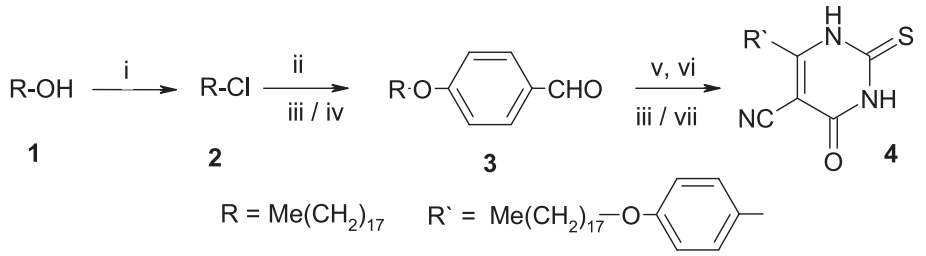
Nonionic surfactants find diverse applications, both in industry and in the home. Their moderate foaming and good detergency are employed in a variety of ways in the leather industry, accelerated soaking and liming are improved by the addition of wetting agents (El-Dougdoug and Ahmed, 2004). The study of the surface active properties of the oxypropylated compounds has been done in an aqueous solution (1wt %, pH = 7) at 25°. 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

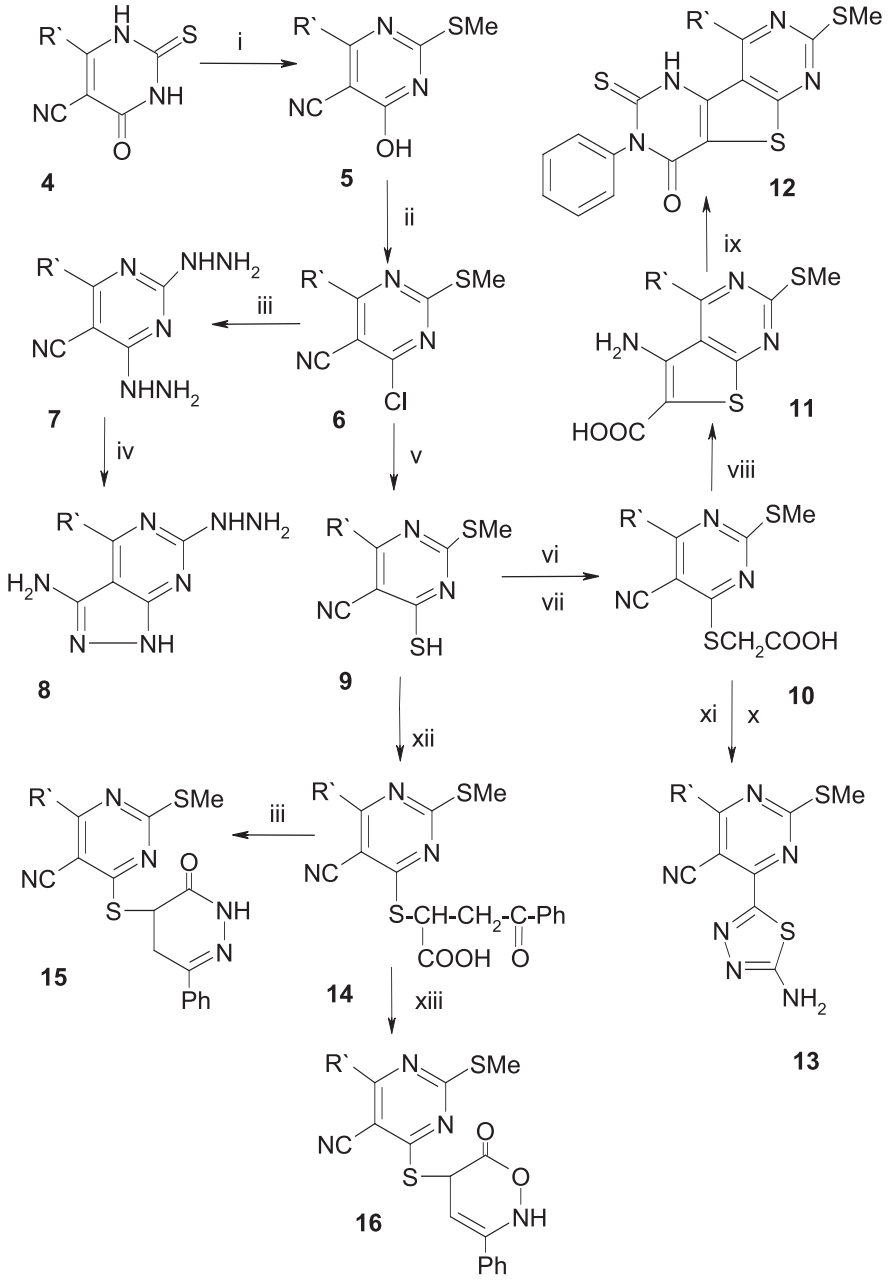
The surface and interfacial tension of the prepared compounds are shown in Table 2. It can be observed that the alkyl chain length gives rise to increased hydrophobic interaction between the alkyl chains and also to increased hydrophobic hydration effects that in turn may reduce the surface tension which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



Scheme I
Reagents: (i) $POCl_3/PCl_5$; (ii) $HOC_6H_4CHO(p)$; (iii) K_2CO_3; (iv) acetone; (v) $NCCH_2COOC_2H_5$; (vi) NH_2CSNH_2; (vii) EtOH



Scheme II
Reagents: (i) MeI; (ii) $POCl_3/PCl_5$; (iii) NH_2NH_2; (iv) BuOH; (v) NH_2CSNH_2; (vi) $ClCH_2COOH$, (vii) AcONa; (viii) EtONa; (ix) PhNCS; (x) $NH_2NHCSNH_2$; (xi) $POCl_3$; (xii) PhCOCH=CH-COOH; (xiii) $NH_2OH.HCl$

Table 1
Reaction conditions of propenoxylated compounds

Compd	Catalyst, wt %	Temperature °C	Propoxylated product	Yield %	Degree of Propenoxylation [a] n*
4	KOH, 0.01 wt %	120-125	17a-c	**70**	5-15
6			18a-c	**72**	5-15
7			19a-c	**65**	5-15
8			20a-c	**75**	5-15
9			21a-c	**70**	5-15
10			22a-c	**80**	5-15
11			23a-c	**72**	5-15
12			24a-c	**62**	5-15
13			25a-c	**70**	5-15
14			26a-c	**73**	5-15
15			27a-c	**67**	5-15
16			28a-c	**75**	5-15

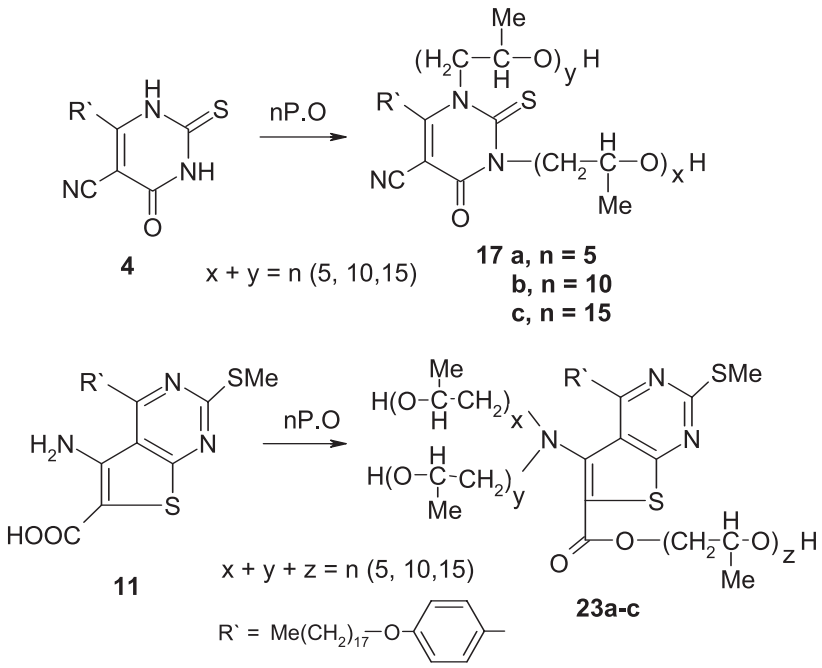
[a] n* Degree of propenoxylation was calculated by weight.

Table 2
Surface properties of nonionic compounds [a]

Compd	n[b]	Surface Tension (dyne/cm) 0.1 %	Interfacial Tension (dyne/cm) 0.1 %	Cloud Point °C 1%	Wetting time (sec.) 1%	Emulsion stability (min.sec)	Foam power (mm) 1%	
							Intial	After 5 min
17a	5	27	7.5	67	65	260: 40	200	190
17b	10	32	8.0	67	90	300: 30	220	205
17c	15	36	8.5	91	123	350: 50	225	210
18a	5	28	8.2	69	90	280: 55	155	149
18b	10	32	8.7	81	115	320: 25	170	158
18c	15	37	9.0	90	132	360: 20	190	173
19a	5	26	9.5	73	80	250: 10	180	165
19b	10	31	10.3	92	110	290: 25	200	189
19c	15	39	11.0	99	135	340: 22	220	205
20a	5	29	11.4	70	100	286: 40	185	163
20b	10	35	12.0	87	115	305: 55	200	184
20c	15	37	12.5	98	126	330: 30	230	210
21a	5	27	6.7	63	85	254: 45	148	125
21b	10	31	7.0	75	100	280: 26	165	136
21c	15	35	7.5	96	120	320: 10	188	145
22a	5	25	8.7	77	36	227: 21	145	124
22b	10	29	9.2	90	42	260: 39	159	139
22c	15	35	10.0	99	48	300: 38	183	148
23a	5	27	8.5	67	30	230: 47	210	190
23b	10	32	9.0	83	31	270: 50	220	205
23c	15	36	9.5	94	36	310: 11	235	214
24a	5	29	7.0	59	32	222: 50	190	174
24b	10	33	7.5	77	35	265: 11	200	183
24c	15	38	8.0	89	35	300: 38	205	191
25a	5	28	8.6	64	35	226: 17	180	166
25b	10	30	9.0	82	40	263: 33	200	182
25c	15	35	9.4	93	45	290: 22	210	190
26a	5	27	8.7	76	39	227: 21	155	128
26b	10	32	9.2	86	45	260: 39	160	132
26c	15	36	10.0	97	48	300: 38	165	146
27a	5	30	7.0	73	32	222: 50	190	174
27b	10	36	7.5	85	35	265: 11	200	183
27c	15	38	8.0	93	35	300: 38	205	191
28a	5	31	8.2	70	90	280: 55	155	149
28b	10	35	8.7	83	115	320: 25	170	158
28c	15	37	9.0	91	132	360: 20	190	173

[a] 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.



Scheme III

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 (*Staphyloccus 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,

Table 3
Biodegradability of the prepared surfactants [a]

Compd	n[a].	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
17a	5	49	62	70	77	86	92	–
17b	10	46	56	69	72	83	88	–
17c	15	40	51	66	72	79	83	–
18a	5	53	65	71	81	93	–	–
18b	10	48	59	69	77	80	91	–
18c	15	45	57	67	74	78	88	–
19a	5	55	55	62	79	87	90	–
19b	10	49	51	59	67	78	88	–
19c	15	47	48	57	63	72	85	–
20a	5	53	58	66	80	82	93	–
20b	10	50	56	63	71	79	96	–
20c	15	49	54	59	68	95	–	–
21a	5	57	62	71	79	85	93	–
21b	10	55	57	69	73	83	90	–
21c	15	52	52	68	71	79	87	–
22a	5	48	60	68	78	89	–	–
22b	10	45	56	66	73	76	98	–
22c	15	41	51	64	70	73	80	–
23a	5	49	66	79	89	96	–	–
23b	10	48	63	73	86	95	–	–
23c	15	43	59	71	79	88	96	–
24a	5	50	62	68	79	92	–	–
24b	10	47	55	63	72	80	93	–
24c	15	43	49	45	65	77	91	–
25a	5	54	54	60	77	80	93	–
25b	10	48	52	57	65	76	90	–
25c	15	45	49	54	61	73	86	–
26a	5	55	63	73	82	78	80	–
26b	10	52	59	70	75	85	92	–
26c	15	49	54	69	73	81	91	–
27a	5	54	63	73	84	95	–	–
27b	10	48	55	67	79	92	–	–
27c	15	45	50	61	72	84	93	–
28a	5	55	67	75	85	95	–	–
28b	10	52	59	71	82	92	–	–
28c	15	50	56	61	75	88	93	–

[a] Error of calculations was: Biodegradation rate = ± 0.5 %.

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 *Entrobacter 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.

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Table 4
Antibacterial activity of the prepared compounds

Compd	*Stophyloccus aureus s*	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomonas aurignosa*	*Escherichia coli*	*Enterobacter aerogenes*
17a	+	+	+	+	+	+
17b	+	–	+	+	+	++
17c	++	–	++	++	+	++
18a	+	+	+	+	+	+
18b	++	–	+	+	+	++
18c	+	+	+	+++	+	+
19a	+	+	+	+	+	+
19b	++	–	++	+	+	++
19c	++	+	++	++	+	++
20a	+	–	+	++	+	++
20b	++	–	+	+	+	+
20c	++	+	+	++	+	++
21a	+	+	+	+	+	+
21b	+	+	+	+	+	+
21c	++	+++	+	++	+	+
22a	++	+	++	++	+	++
22b	++	++	++	++	+	++
22c	++	+	++	++	+	++
23a	++	+	++	+++	+	++
23b	++	+	++	++	+	++
23c	++	++	++	++	+	++
24a	++	+	+	++	+	++
24b	++	+	++	++	+	++
24c	++	++	++	+++	+	++
25a	++	+	+	++	+	++
25b	++	+	++	++	+	++
25c	++	++	++	++	+	++
26a	+	+	+	++	+	+
26b	++	+	++	++	+	++
26c	++	+++	++	+++	+	++
27a	+	+	+	+	+	+
27b	++	+	++	++	+	++
27c	++	+++	++	+++	+	++
28a	+	+	+	+	+	+
28b	++	+	++	++	+	++
28c	++	+++	++	++	+	++
Sulphadiazine	++	++	++	++	++	+++

[a] Error of calculations was: Biodegradation rate = ± 0.5 %.

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Table 5
Antifungal activity of the prepared compounds

Compd	*Aspergillus niger*	*Penicillium italicum*	*Fusarium oxysporum*
17a	+	+	+
17b	+	+	++
17c	+	+	++
18a	+	+	+
18b	+	+	++
18c	+	+	++
19a	+	+	+
19b	+	+	++
19c	+	+	++
20a	+	+	+
20b	+	+	++
20c	+	+	++
21a	+	+	+
21b	+++	+	++
21c	+	+	++
22a	+	+	+
22b	+	+	++
22c	+	+	++
23a	+	+	+
23b	++	+	++
23c	+	+	++
24a	+	+	+
24b	++	+	++
24c	+	+	++
25a	+	+	+
25b	+++	+	++
25c	++	+	++
26a	+	+	+
26b	+	+	++
26c	++	+	++
27a	+	+	+
27b	+	+	++
27c	+	+	++
28a	+	+	+
28b	+	++	++
28c	+	+	++
Sulphadiazine	++	++	++

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