Synthesis and evaluation of $\alpha$-hydroxy fatty acid-derived heterocyclic compounds with potential industrial interest

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2. MATERIALS AND METHODS

The melting points reported are uncorrected. IR spectra in KBr were measured on a Pye-Uncam SP-1000 infrared spectrophotometer on a KBr disk or nujol. The $^1$H NMR spectra were obtained on a Varian EM-390-60 MHz spectrometer in DMSO as the solvent. Tetramethylsilane TMS served as an internal reference and chemical shifts are expressed as $\delta$ (ppm). UV spectra were registered with a Perkin-Elmer 550 S UV-Vis spectrophotometer using absolute ethanol as solvent. Mass spectra were recorded on a GC/MS Finning-MAT. Microanalyses were performed by the Micro analytical Unit at Cairo University. All the compounds gave satisfactory elemental analyses. Thin layer chromatography (TLC) was carried out on silica gel (MN-Kieselgel G., 0.2 mm thickness) and the plates were scanned under 254 nm ultraviolet light. Antimicrobial and antifungal activity tests were carried out by the microbiology Lab., Faculty of Science, Benha University, Egypt.

2.1. Synthesis of 2-(1-hydroxyheptadecyl)-4H-3,1-benzoazin-4-one (3)

2-Hydroxyheptadecanoyl chloride (2, 0.01mol) and anthranilic acid (0.01mol) in dry pyridine (30 ml) was refluxed for 3 h. The reaction mixture was
cooled and poured into cold diluted HCl (10 ml). The separated solid was filtered off and crystallized from toluene to yield, 80%. mp = 86-88 °C. IR: v 3420 (OH), 2910 and 2860 (CH aliphatic), 3014 (CH aromatic), 1681 (CO) and 1589 cm–1 (C=N). 1H NMR (CDCl3): δ 0.96 (t, 3H, CH3), 1.29-1.33 (m, 30H, CH2 of alkyl chain), 3.2 (s, 1H, CH2), 7.5-8.1 (m, 4H, aromatic) and 9.7 (s, 1H, OH). MS: m/z = 357 (59.9 %) assigned to (M+- CO2), and m/z = 59 (100 %). Anal. Calcd. for C27H41ClN2O3 (492.11): C, 65.90; H, 8.60; N, 8.54.

2.2. Synthesis of 2-(1-hydroxyheptadecyl)-quinazolin-4(3H)-one (4)

A mixture of 3 (0.01 mol) and formamide (0.015 mol) was refluxed in ethanol (30 ml) for 3 h and then poured into water (20 ml). After concentration, the separated solid was filtered off and crystallized from ethanol to give 4. Yield 76%, mp = 75-77 °C. IR: v 3450 (OH), 3320 (NH), 2920 and 2850 (CH aliphatic), 1680 cm–1 (CO). 1H NMR (CDCl3): δ 0.95 (t, 3H, CH3), 1.2-1.3 (m, 30H, CH2 in chain), 3.3 (s, 1H, CH2OH), 8.2 (brs,1H, NH), 7.3-7.8 (m, 4H, aromatic) and 9.7 (s, 1H, OH). Anal. Calcd. for C25H40N2O2 (401.61): C, 74.96; H, 10.06; N, 6.99. Found C, 74.80; H, 9.83; N, 3.52 %.

2.3. Synthesis of 3-(2-chloroacetyl)-2-(1-hydroxyheptadecyl)-quinazolin-4(3H)-one (5)

A mixture of 4 (0.01 mol) and chloroacetyl chloride (0.01 mol) was refluxed in N,N-dimethylformamide (DMF) (30 ml) for 3 h. The mixture was then poured into water (20 ml) and the precipitated solid was filtered off, dried and crystallized from benzene to give 5. Yield 76%, mp = 93-95 °C. IR: v 3456 (OH), 2920 and 2850 (CH aliphatic), 1671 and 1699 (CO), 1600 cm–1 (C=N). 1H NMR (CDCl3): δ 0.95 (t, 3H, CH3), 1.25-1.33 (m, 30H, CH2 of alkyl chain), 4.25 (s, 2H, CH2), 3.2 (s, 1H, CH2OH), 7.5-7.9 (m, 4H, aromatic) and 2.0 (s, 1H, OH). Anal. Calcd. for C25H41ClN2O2 (400.61): C, 70.76; H, 10.06; N, 6.95. Found C, 77.00; H, 9.12; N, 3.52 %.

2.4. Synthesis of 3-(2-hydrazinoacetyl)-2-(1-hydroxyheptadecyl)-quinazolin-4(3H)-one (6)

A mixture of 5 (0.01 mol) and hydrazine hydrate (0.015 mol) in dry benzene (30 ml) was refluxed for 4 h. Then the solution was poured into water (20 ml) and the precipitated solid was filtered off, dried and crystallized from ethanol to yield 6. Yield 65 %, mp = 92-94 °C. IR: v 3350 (OH), 3329 (NH), 2921, 2849 (CH aliphatic), 1690 (CO), and 1600 cm–1 (C=N). 1H NMR: (CDCl3) δ 0.95 (t, 3H, CH3), 1.29-1.33 (m, 30H, CH2 of alkyl chain), 3.1 (s, 1H, CH2OH), 7.4-7.9 (m, 4H, aromatic), 8.2 (brs,1H, NH) and 9.5 (s, 1H, OH). MS: shows a molecular ion peak at m/z = 454 (41.12 %). Anal. Calcd. for C27H42ClN3O3 (492.11): C, 72.22; H, 7.49; N, 10.15 %.

2.6. Synthesis of 3-amino-2-(1-hydroxyheptadecyl)-quinazolin-4(3H)-one (8)

A solution of 3 (0.01 mol) and hydrazine hydrate (0.015 mol) in dry benzene (30 ml) was refluxed for 4 h. Then the solution was poured into water (20 ml) and the precipitated solid was filtered off, dried and crystallized from ethanol to give 8. Yield 78 %, mp= 92-94 °C. IR: v 3350 (OH), 3329 (NH), 2921, 2849 (CH aliphatic), 1690 (CO), and 1600 cm–1 (C=N). 1H NMR: (CDCl3) δ 0.95 (t, 3H, CH3), 1.29-1.33 (m, 30H, CH2 of alkyl chain), 3.1 (s, 1H, CH2OH), 7.4-7.9 (m, 4H, aromatic), 8.2 (brs,1H, NH) and 9.5 (s, 1H, OH). Anal. Calcd. for C27H42N4O3 (454.62): C, 71.22; H, 9.98; N, 10.15 %.

2.7. Synthesis of 3-chloro-N-[2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl]acetamide (9)

A solution of 8 (0.01 mol) and chloroacetyl chloride (0.01 mol) in pyridine (15 ml) was refluxed for 2h and then poured onto ice/HCl (20 ml). The product was filtered and crystallized from toluene to yield 9. Yield 65 %, mp = 105-107 °C. IR: v 3338, 3170 (OH and NH), 2920 and 2850 (CH aliphatic), 1694 and 1666 cm–1 (CO). 1H NMR: δ 0.85 (t, 3H,CH3), 1.2-1.5 (m, 30H, CH2 of alkyl chain), 3.4 (s, 1H, CH2OH), 4.24 (s, 2H, CH2), 7.3-7.8 (m, 4H, aromatic), 8.0 and 9.3 (s, 3H, NH) and 9.7 (s, 1H, OH). MS: shows a molecular ion peak at m/z = 492 (54.1 %). Anal. Calcd. for C27H42ClN2O2 (449.62): C, 65.95; H, 8.57; N, 8.61 %.

2.8. Synthesis of 6-(1-hydroxyheptadecyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-3(4H)-one (10)

A solution of 8 (0.01 mol) and ammonium acetate (0.01mol) in acetic acid (30 ml) was refluxed for 3 h and then poured into water (20 ml). After concentration, the separated solid was filtered off and crystallized from ethanol to give 10.
Yield 75 %, mp = 73-75 °C. IR: ν 3430 (OH), 3230 (NH), 2870 and 2980 (CH), 1660 (CO) and 1605 cm⁻¹ (C=N). ¹HNMR: (CDCl₃) δ 0.96 (t, 3H, CH₃), 1.29-1.33 (m, 30H, CH₂ of alkyl chain), 4.40 (s, 2H, CH₂), 3.2 (s, 1H, CH-OH), 7.3-7.6 (m, 4H, aromatic), 8.0 (brs, 1H, NH) and 2.0 (s, 1H, OH).

MS: shows the molecular ion peak at m/z = 454 (44.11 %). Anal. Calcd for C₂₇H₄₂N₄O₂ (454.66): C, 71.33; H, 9.31; N, 12.32. Found C, 71.35; H, 9.34; N, 12.35 %.

2.9. Synthesis of 6-(1-hydroxyheptadecyl)-3,4-dihydro-[1,2,4]triazino[2,3-c]quinazolin-2-one (11)

A solution of 8 (0.01mol) and chloroaceticamide (0.015 mol) was refluxed for 3 h in DMF (30 ml). The solution was then poured into water (20 ml). The precipitated solid was filtered off, dried and crystallized from ethanol to give 11. Yield 75 %, mp = 75-77 °C. UV: λ max = 330 (450), 314 (1450).

Scheme I

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a) Compounds from 3 to 15 were propenoxylated at any active hydrogen (OH, NH and NH₂) to give products from 16a-c to 28a-c, respectively.
2.10. Synthesis of 1-[2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl]-3-phenylthiourea (12)

A solution of 8 (0.01 mol) and phenyl isothiocyanate (0.01 mol) in benzene (30 ml) was refluxed for 3 h. After concentration, the residue was crystallized from butanol to give 12. Yield 65 %, mp = 107-109 °C. IR: ν 3440 (OH), 3380 and 3200 (NH nonbonding and bonded), 2960 and 2870 (CH), 1670 (CO), 1620 (C=N) and 1230 cm–1 (CS). 1HNMR (CDCl3): δ 0.9 (t, 3H, CH3), 1.2-1.3 (m, 30H, CH2 in chain), 3.1 (s, 1H, CH–OH), 4.8 (brs, 1H, NH), 6.4-7.9 (m, 4H, aromatic) and 9.5 (s, 1H, OH). Anal. Calcd for C27H43N3O3: C, 71.33; H, 9.31; N, 12.32. Found C, 71.39; H, 9.27; N, 12.28 %.

2.11. Synthesis of 3-(2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione (13)

A solution of 12 (0.01 mol) and malonic acid (0.01 mol) in acetyl chloride (40 ml) was refluxed for 3 h and then poured into water (20 ml). The separated solid was filtered off and crystallized from benzene to give 13. Yield 60 %, mp = 78-80 °C. IR: ν 3430 (OH), 3410 (OH), 3340 (NH), 2910-2860 (CH aliphatic), 3050 (CH aromatic) and 1649 cm–1 (C=N). 1HNMR (CDCl3): δ 0.9 (t, 3H, CH3), 1.3-1.7 (m, 30H, CH2), 4.3 (s, 1H, CH–OH), 7.32-8.11 (m, 9H, aromatic) and 2.0 (s, 1H, OH). MS: shows the molecular ion peak at m/z = 619.8 (34.16 %). Anal. Calcd for C32H46N4O4S (550.81): C, 70.86; H, 9.47; N, 9.18. Found C, 70.91; H, 9.51; N, 9.15 %.

2.12. Synthesis of N-(2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl)benzamide (14)

A solution of 13 (0.01 mol) in dry acetone (30 ml) was refluxed for 3 h. The solvent was removed by evaporation to obtain a solid which was crystallized from benzene-hexane to give 14. Yield 65 %, mp = 78-80 °C. IR: ν 3440 (OH), 3320 (NH), 6.46-7.9 (m, 4H, aromatic) and 9.5 (s, 1H, OH). Anal. Calcd for C27H42N4O2S: C, 71.33; H, 9.31; N, 12.32. Found C, 71.39; H, 9.27; N, 12.28 %.

2.13. Synthesis of 1-(2-phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)heptadecan-1-ol (15)

A solution of 14 (0.01 mol) and ammonium acetate (0.01 mol) in acetic acid (30 ml) was refluxed for 3 h and then poured into water (20 ml). After concentration, the separated solid was filtered off and crystallized from butanol to give 15. Yield 60 %, mp = 81-83 °C. IR: ν 3430 (OH), 2910-2860 (CH aliphatic), 3050 (CH aromatic) and 1589 cm–1 (C=N). 1HNMR: δ 0.95 (t, 3H, CH3), 1.2-1.3 (m, 30H, CH2), 4.3 (s, 1H, CH–OH), 7.32-8.11 (m, 9H, aromatic) and 2.0 (s, 1H, OH). MS: shows the molecular ion peak at m/z = 438 (37.16 %). Anal. Calcd for C32H46N4O2S (438.66): C, 73.91; H, 9.65; N, 12.77. Found C, 73.91; H, 9.61; N, 12.80 %.

2.14. Conversion of the prepared compounds (3-15) to nonionic surfactants (16a-c-28a-c)

They are prepared by the addition of n moles of propylene oxide (n = 5, 10, 15) to one mol of a suitable product using KOH as catalyst. A complete description of the procedure is given in Morgos (1983). The reaction conditions are given in Table I. The amount of propylene oxide which reacted and the average degree of propenoxylolation were determined through the increment in mass of the reaction mixture and also, by 1HNMR protons. These products were confirmed by spectroscopic methods. The addition of propylene oxide gave a mixture of propenoxylated products whose structures were shown through IR and 1HNMR. IR spectra to be two broad bands at 1100 and 950 cm–1. The characteristic for νC-O-C ether linkage of polypropenoxy chain and 1HNC spectra showed the protons of propenoxy group at δ 3.2-3.7 (m, CH2CH2(CH3)2-O)-.

2.15. Determination of the performance properties

2.15.1. Surface and interfacial tensions

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

2.15.2. Cloud point

Cloud point was determined by gradually heating a surfactant solution (1.0 wt %) in a temperature controlled bath, 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 became clear again (Wiel et al., 1963).

2.15.3. Wetting time

Wetting time was determined by immersing a sample of cotton fabric in a 1.0 wt % aqueous solution of surfactants (Draives et al., 1931).
### Table I

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Degree of propenoxylation was calculated by weight

### Table II

#### Surface properties of nonionic compounds

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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
2.15.4. Foaming properties

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 glass stopper at 25 °C. The solution was allowed to stand for 30 seconds, and then, the foam height was measured.

2.15.5. Emulsification stability

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 it took 9 ml of an aqueous layer to separate from the emulsion once shaking had stopped. (Takeshi, 1970).

2.16. Biodegradability

Biodegradability was evaluated by surface tension measurements which were taken daily on each sample during the degradation test. Biodegradation (Eter et al., 1974) percent (D) for each sample was calculated using the following equation: \[ D = \left( \log \frac{\gamma_t}{\gamma_o} \right) \times 100, \]
where \( \gamma_t \) = surface tension at zero time, \( \gamma_o \) = surface tension of blank experiment at time \( t \) (without sample).

2.17. Biological activity

The antimicrobial activities of the synthesized surfactants were determined in vitro using the hole plate and filter paper disc method (Rosen, 1989). Compounds were dissolved in 10% acetone at each sample concentration (125, 250, 500 µg/ml). Agar plates were inoculated uniformly from a fresh broth culture of Gram +ve, Gram –ve bacteria and fungi. The disks were incubated at 28 °C for 24 h, and the formed inhibition zones were measured in mm.

3. RESULTS AND DISCUSSION

3.1. Synthesis

2-Hydroxyheptadecanoyl chloride (2) was prepared as described (Eissa et al., 2003; Amin, 2004). The treatment of 2 with anthranilic acid in pyridine gave 2-(1-hydroxyheptadecyl)-4H-3,1-benzoazin-4-one (3). The reaction of 3 with formamide gave 2-(1-hydroxyheptadecyl)-3H-quinazolin-4-one (4). The treatment of 4 with chloroacetyl chloride in (DMF) gave 6-(1-hydroxyheptadecyl)-2H-quinazo-lin-3(4H)-one (10). At the same time, the reaction of 8 and chloroacetamide in DMF gave 6-(1-hydroxyheptadecyl)-3,4-dihydro-[1,2,4] triazino [2,3-c] quinazolin-2-one (11).

When compound 3 reacted with hydrazine hydrate it gave the amino quinazolinolone 8. The reaction of 3 with chloroacetyl chloride in refluxing pyridine gave 3-chloro-N-[2-(1-hydroxyheptadecyl)-4-oxo-4H-quinazolin-3-yl]acetamide (9) which was treated by ammonium acetate-acetic acid to yield 6-(1-hydroxyheptadecyl)-2H-[1,2,4] triazino[2,3-c] quinazo-lin-3(4H)-one (10). At the same time, the reaction of 8 and chloroacetamide in DMF gave 6-(1-hydroxyheptadecyl)-3,4-dihydro-[1,2,4] triazino [2,3-c] quinazolin-2-one (11).

In addition, the treatment of 8 with phenyl isothiocyanate in benzene gave 1-[2-(1-hydroxyheptadecyl)-4-oxo-quinazolin-3(4H)-yl]-3-phenylthiourea (12) which was refluxed with malonic acid in acetylchloride giving 3-(2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione (13).

Finally, when compound 8 reacted with benzoic chloride it gave N-[2-(1-hydroxyheptadecyl)-4-oxoquinazolin-3(4H)-yl]benzamide (14) which was treated by ammonium acetate-acetic acid to give 1-(2-phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)heptadecan-1-ol (15).

3.2. Conversion of the prepared compounds (3-15) to nonionic surfactants (16a-c -28a-c)

The structure of a surface active agent requires a hydrophilic component. This is accomplished through the condensation of alkylene oxide at any active terminal group. Thus, the addition of propylene oxide gave mixtures of propenoxylated products whose structures were confirmed by IR and 1HNMR spectroscopy.

3.2.1. Surface active properties

The study of the surface active properties of the oxypropylated compounds was done in an aqueous solution (1wt %, pH = 7) at 25 °C. The results are listed in Table II.

3.2.1.1. Surface and interfacial tensions

The surface and interfacial tensions of the prepared compounds are shown in Table II. It can be observed that the new nonionic surfactants have pronounced surface activity. In general, the surface and interfacial tensions increase with an increase in the molecular weight of the hydrophobic moiety (Eissa et al., 2003). The data given in Table II shows that the values of surface and interfacial tensions increased with the increase in the number of propylene oxide units added to the molecule.

3.2.1.2. Cloud point

A very important factor in making the most efficient use of nonionic surfactants in an aqueous system is an understanding of the property called cloud point. The data (Table II) show that the cloud point...
increases with an increasing number of propenoxy groups per hydrophobic molecule. The cloud point of the prepared surfactants is less than 100 °C.

3.2.1.3. Wetting time

All the prepared compounds showed a decrease in the wetting time with an increasing number of propylene oxide units in the molecule. The synthesized surfactants, even those with low propylene oxide content, were efficient wetting agents.

3.2.1.4. Foam power

Foaming of the nonionic compounds was also studied. The foam height of the prepared surfactants increases with an increase in the propylene oxide units per molecule of surfactant. The low foaming power could have an application in the dyeing industry (Somya et al., 1998).

3.2.1.5. Emulsion stability

Studies are still being carried out on the utilization of surfactants in emulsions formation, which is of immense importance for technological development. It was proven that the prepared surfactants exhibit good emulsifying properties. Emulsion stability increases with a decreasing number of propylene oxide units. These results might lead to the application of the surfactants of choice in the development of pesticides and cosmetics.

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a) n is the number of moles of propylene oxide added to the chosen compound

Error of calculations was: Biodegradation rate = ± 0.5 %
SYNTHESIS AND EVALUATION OF α-HYDROXY FATTY ACID-DERIVED HETEROCYCLIC COMPOUNDS WITH POTENTIAL INDUSTRIAL...

3.2.2. Biodegradability

The trend of degradation in river die-away tests was followed by surface tension measurements. The results are given in Table III. 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 degradable than those containing a higher proportion.

3.2.3. Biological activity

As shown in Table IV most of the synthesized surfactants have remarkable antimicrobial activity towards the selected bacteria and fungi. The presence of heterocyclic moiety in the prepared nonionic surfactant molecule revealed an increase in biological activity. It is therefore clear that these surfactants were effective and inhibited the growth of all the microorganisms tested.

### 4. CONCLUSION

It can be concluded that all the prepared nonionic surfactants have good emulsifying properties in non edible media as insecticides and pesticides.
BIBLIOGRAPHY


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