Potential Biosignificant Interest and Surface Activity of Efficient Heterocyclic Derivatives

Refat El-Sayed¹, ²* and Ismail Althagafi²

¹ Chemistry Department, College of Applied Sciences, Umm Al-Qura University, 21955 Makkah, Saudi ARABIA
² Chemistry Department, Faculty of Science, Benha University, Benha, EGYPT

Abstract: Some functionalized pyridine and fused system derivatives were synthesized using enaminonitrile derivative 5 as a starting material for the reaction, with various reagents under different conditions. Propoxylation of these compounds using different moles of propylene oxide (3, 5 and 7 moles) leads to a novel group of surface active agents. The antimicrobial and surface activities of the synthesized compounds were investigated. Most of the evaluated compounds proved to be active as antibacterial and antifungal agents and showed good surface activity, which makes them suitable for diverse applications such as the manufacturing of emulsifiers, cosmetics, drugs, pesticides, etc. Additionally, biodegradation testing exhibits significant breakdown within six to seven days, and hence, lowers the toxicity to human beings and becomes environmentally friendly.

Key words: synthesis, antimicrobial and surface activities

1 INTRODUCTION

Recently, various bioactive compounds, their assemblies and related nanostructured materials have been paid much attention¹–³, especially when employing many heterocyclic compounds in treating infectious diseases because of their specific activity. Their usage in the treatment is attributed to their inherent toxicity to various pathogens⁴. Pyridine derivatives are an interesting class of heterocycles due to their synthetic versatility and effective biological activities such as antimicrobial⁵–⁷, anticancer⁸, anticonvulsant⁹, antiviral¹⁰, anti-HIV¹¹, antimycobacterial and antifungal activities¹². Pyrido[2,3-d]pyrimidines derivatives are heterocyclic ring systems of substantial interest due to numerous biological activities associated with this support¹³. Pyridine derivatives are an important class of heterocycles found in various natural products, functional materials and active pharmaceuticals¹⁴. Moreover, the pyrazolo[3,4-b]pyridine structure shows a broad variety of biological activity¹⁵. Some heterocyclic derivatives have been found to regulate the circulatory system and possess antiviral¹⁶ and antimicrobial properties¹⁷. Pyrazolopyrimidine derivatives possess extensive applications in the medicine and agriculture fields and have useful properties as antimetabolites in purine biochemical reactions¹⁸–²⁰.

On the other hand, fatty derivatives are easily ingested by the human body and will focus on the synthesis of many heterocyclics, substituted with fatty residue, to make more a gradual intake of heterocycles in the human body and produce an amount of biological properties²¹. Enormous applications of fatty heterocyclic derivatives act as biologically active agents²². Oleo chemicals are essential in various industries such as surfactants, plasticizers, coatings, lubricant additives (anti-block and anti-slip additives), cosmetics, soaps, detergents, textiles, plastics, pharmaceuticals, organic pesticides and are used in cosmetic formulations²³–²⁸.

There is encouragement of the various biological activities of the heterocyclic moieties, as our program intended to develop new selective and environmentally friendly methodologies for the preparation of heterocyclic derivatives²⁹–³² and investigations of their physico-chemical properties and antimicrobial activities. Herein, we found that enaminonitrile derivative 5 is a highly versatile and useful building block for the synthesis of a wide range of certain functionalized pyridine and fused pyridine derivatives.

2 EXPERIMENTAL

All melting points are in degree centigrade and were determined on a Gallenkamp electronic melting point appara-
R. E.-Sayed and I. Althagafi
J. Oleo Sci. 65, (2) 177-192 (2016)

was then filtered, washed and recrystallised from ethanol.

A mixture of 1.5 mmol

ArH

arom

ʣ

1.5 mmol

was added and the entire mixture was stirred for two hours

1.5 mmol

1.5 mmol

was slowly added and the entire mixture was stirred for two hours until it became cloudy. Then the mixture was slowly poured into water (400 mL), constantly stirred and kept in the refrigerator for 24 hours. The obtained precipitate 3 was then filtered, washed and recrystallised from ethanol.

Yellow crystals yielded (0.94g, 70%) and m.p. 225–227°C. IR (ν/cm⁻¹): 3398 (OH), 3338, 3321 (NH2), 3072 (str.CH-aram), 1668 (str.CO) and 1604 (CH=CH). 1H NMR (CDCl₃): δ 3.68(s, 3H, OCH3), 6.28(s, 2H, NH2), 7.25–7.64(m, 7H, ArH), 7.78, 7.80(d, 1H, J = 12, CH = CH). Anal. Calcd. for C₃₇H₅₀N₄O₃: C, 76.22; H, 9.22; N, 5.20. Found: C, 71.61; H, 5.61; N, 5.20.

Step 2. Formation of N-(4-((4-hydroxy-3-methoxyphenyl)prop-2-enyl)phenyl)stearamide (4)

Equimolar amounts of chalcone derivative 2 (0.4g, 1.5 mmol) and a catalytic amount of triethylamine in dry acetone (20 mL) maintained at −10°C was added dropwise while stirring a solution of stearoyl chloride 2 (0.45 g, 1.5 mmol) in dry acetone (15 mL) over a period of one hour. The reaction mixture was stirred overnight. The product obtained upon pouring onto the ice and water mixture, which contained drops of hydrochloric acid, was collected through recrystallization from ethanol. Yellow crystals yielded (0.29 g, 74%), m.p. 165–167°C, IR (ν/cm⁻¹): 3378–3317 (OH and NH), 3077 (str.CH-aram), 2915–2848 (CH-alamiph.) 1701, 1663 (str.CO) and 1598 (CH=CH). 1H NMR (δ, ppm): 0.88(t, 3H, CH3), 1.19–1.57(s, 32H, CH2 aliphatic), 3.90(s, 3H, OCH3), 5.36(s, 1H, OH), 6.97, 6.99(d, 1H, J = 13, CH = CH), 7.19-7.87(m, 7H, ArH) and 9.77(s, 1H, NH). Anal. Calcd. for C₃₉H₅₆N₂O₃ (535.76): C, 76.22; H, 9.22; N, 2.61. Found: C, 76.53; H, 9.48; N, 2.94.

Step 3. Formation of N-(4-((6-amino-5-cyano-4-(4-hydroxy-3-methoxyphenyl)pyridin-2-yl)phenyl)stearamide (5)

To a solution of 4 (0.8 g, 1.5 mmol) in ethanol (20 mL), malononitrile (0.07 g, 1.5 mmol) and ammonium acetate (0.601 g, 8 mmol) were added. The content was heated under reflux for 12 hours. The resulting content was poured onto the ice and water; thus, the solid that separated was filtered, washed with cold water and crystallized in ethyl alcohol. Pale yellow crystals yielded (0.62g, 78%), m.p. 133–135°C, IR (ν/cm⁻¹): 3410–3224 (OH, NH and NH), 3072 (CH-alamiph.), 2918–2849 (CH-alamiph.), 2218 (CN), 1669 (str.CO) and 1580 (C=N). 1H NMR (δ, ppm): 0.91 (t, 3H, CH3), 1.27–1.67(s, 32H, CH2 aliphatic), 3.97(s, 3H, OCH3), 5.47(s, 1H, OH), 6.95(s, 2H, NH2), 7.26–7.68(m, 7H, ArH), 7.84(s, 1H, CH of pyridine ring) and 8.12(s, 1H, NH). 13C NMR (δ, ppm): 14.15, 18.25, 18.50, 22.71, 24.86, 25.47, 26.47, 29.14, 29.27, 29.30, 29.38, 29.49, 29.63, 29.69, 29.71, 31.94, 33.86, 37.87, 55.44, 114.41, 118.91, 119.79, 127.63, 129.87, 138.62, 142.18, 144.51, 148.99, 153.61, 157.22, 164.65, 177.18. Anal. Calc. for C₃₇H₅₀N₄O₃ (598.82): C, 74.21; H, 8.42; N, 9.36. Found: C, 74.55; H, 8.61; N, 9.09.

2.1.2 Synthesis of N-(4-(5,7-dimino-6-cyanode-4-(4-hydroxy-3-methoxyphenyl)-1,8-naphthyridin-2-yl)phenyl)stearamide (6)

A mixture of 5 (0.89 g, 1.5 mmol) and malononitrile (0.07 g, 1.5 mmol) was added to freshly prepared sodium ethoxide solution. The reaction mixture was heated under reflux for 8 hours and left to cool overnight. The obtained solid product was collected by filtration, washed and crystallized from ethanol. Brown solid yielded (0.65g, 73%), m.p. 117–119°C, IR (ν/cm⁻¹): 3388–3196 (OH, 2NH2 and NH), 3070 (CH-alamiph.), 2916–2848 (CH-alamiph.), 2196(CN), 1691 (str.CO) and 1576, 1517 (C = N). 1H NMR (δ, ppm): 0.87(t, 3H, CH3), 1.18–1.58(s, 32H, CH2 aliphatic), 3.94(s, 3H, OCH3), 5.43(s, 1H, OH), 6.71, 6.93(s, 4H, 2NH2), 7.28–7.60(m, 8H, ArH and CH of pyridine ring), 7.66(s, 1H, CH of pyrimidine ring) and 7.67(s, 1H, NH). Anal. Calc. for C₃₉H₅₆N₂O₃ (664.88): C, 72.26; H, 8.78; N, 12.64. Found: C, 72.49; H, 8.08; N, 12.43.

2.1.3 Synthesis of N-(4-((4-amino-5-(4-hydroxy-3-methoxyphenyl)pyridin-2-yl)phenyl)stearamide (7)

Equimolar amounts of 5 (0.89 g, 1.5 mmol) and formamide (5 mmol) were mixed in dimethylformamide (30 mL), followed by a few drops of piperidine. The reaction mixture was refluxed for 6 hours, cooled and poured into ice-cold water, and neutralized by diluted hydrochloric acid for complete precipitation. The precipitated solid was filtered off, dried and crystallized from aqueous ethanol. A pale brown solid yielded (0.57g, 65%), m.p. 109–111°C, IR (ν/cm⁻¹): 3410–3135 (OH, NH and NH), 2915–2848 (CH-alamiph.), and 1691 (str.CO). 1H NMR (δ, ppm): 0.81(t, 3H, CH3), 1.17–1.66(s, 32H, CH2 aliphatic), 3.79(s, 3H, OCH3),
Synthesis of Biosignificant Heterocyclic Derivatives

J. Oleo Sci. 65, (2) 177-192 (2016)

5.07 (s, 1H, OH), 6.11 (s, 2H, NH2), 6.75 (s, 1H, CH of pyridine ring), 7.19–7.63 (m, 7H, ArH) and 7.91 (s, 1H, CH of pyrimidine ring) and 8.04 (s, 1H, NH). 1H NMR (δ, ppm): 1.17–1.66 (s, 32H, CH2 aliphatic), 3.66 (s, 3H, OCH3), 4.95 (s, 1H, OH), 6.11, 6.75 (s, 2H, 2NH), 7.19–7.63 (m, 7H, ArH), 7.91 (s, 1H, CH of pyridine ring) and 8.04 (s, 1H, NH). Anal. Calc. for C16H11NO2S (674.96): C, 67.62; H, 7.47; N, 8.30; S, 9.50. Found: C, 67.84; H, 7.63; N, 8.54; S, 9.77.

2.1.7 General procedure for synthesis of pyrimidine derivatives (11, 12)

A mixture of 5 (0.89 g, 1.5 mmol) and urea (0.1 g, 1.5 mmol) or thiourea (0.11 g, 1.5 mmol) in absolute ethanol (20 mL) and sodium ethoxide (0.03 g sodium metal in 20 mL absolute ethanol, 5 mmol) was heated under reflux for 6 hours. The reaction mixture was left to cool at room temperature, then poured into ice-cold water (50 mL) and neutralized with diluted hydrochloric acid. The separated material was filtered off and recrystallized from ethanol.

N-(4-(4-aminophenyl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)phenyl stearamide (11)

Pale orange solid yielded (0.45 g, 51%), mp 103–105°C; IR (v/cm−1): 3397–3188 (OH and NH), 3291–2916 (CH-aliph.), 1669 (str. CO), 1594 (C=S), 1212 (C=S), 1101 (C=S). 1H NMR (δ, ppm): 0.88 (t, 3H, CH3), 1.77–1.83 (m, 7H, ArH), 2.83–7.66 (m, 7H, ArH), 7.96 (s, 1H, CH of pyrimidine ring) and 8.03, 8.84 (s, 2H, 2NH). Anal. Calc. for C16H11NO2S (674.96): C, 67.62; H, 7.47; N, 8.30; S, 9.50. Found: C, 67.84; H, 7.63; N, 8.54; S, 9.77.

N-(4-(4-amino-5-(4-hydroxy-3-methoxyphenyl)-2-thioxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)phenyl) stearamide (12)

Brown powder yielded (0.51 g, 58%), mp 114–116°C; IR (v/cm−1): 3389–3142 (OH and 2NH), 2915–2848 (CH-aliph.), 1692 (str. CO), 1595 (C=N), 1185 (C=S). 1H NMR (δ, ppm): 0.86 (t, 3H, CH3), 1.23–1.58 (s, 32H, CH2 aliphatic), 3.67 (s, 3H, OCH3), 4.58 (s, 1H, OH), 6.87 (s, 2H, NH2), 7.00–7.56 (m, 7H, ArH), 7.88 (s, 1H, CH of pyrimidine ring) and 10.87 (s, 1H, NH). Anal. Calc. for C16H11NO2S (674.96): C, 67.62; H, 7.47; N, 8.30; S, 9.50. Found: C, 67.84; H, 7.63; N, 8.54; S, 9.77.

2.1.8 General procedure for reaction of enaminoitrile derivative 5 with o-substituted aniline

An equimolar amount of 5 (0.89 g, 1.5 mmol), o-phenylenediamine, or o-aminophenol in absolute ethanol (30 mL) in the presence of a catalytic amount of piperidine (four drops) was heated under reflux for 30 hours. The reaction mixture was concentrated to its half volume and then left to cool at room temperature overnight. The solid products were filtered off and recrystallized from ethanol.
N-(4-(6-amino-5-(1H-benzo[d]imidazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl) pyridin-2-yl)phenyl) stearamide (13).

Brown powder yielded: [(0.58 g, 66%), mp 156–158°C; IR (v/cm⁻¹): 3394–3178 (OH, NH2 and 2NH), 2915–2848 (CH-aliph.), 1693 (str. CO), 1519 (C=N). ¹H NMR (δ, ppm): 0.87 (t, 3H, CH₃), 1.24–1.58 (s, 32H, CH₂ aliphatic), 3.91 (s, 3H, OCH₃), 5.35 (s, 1H, OH), 6.06 (s, 2H, NH₂), 6.87–7.58 (m, 12H, ArH and CH of pyridine ring) and 10.39 (s, 1H, NH). Anal. Calc. for C₄₃H₅₅N₅O₃: C, 71.93; H, 8.32; N, 6.80. Found: C, 71.68; H, 8.07; N, 6.58.

2.1.11 Synthesis of N-(4-(4-acetyl-5-amino-4-(4-hydroxy-3-methoxyphenyl)-7-methyl-1,8-naphthyridin-2-yl) phenyl) stearamide (17)

A solution of 5 (0.89 g, 1.5 mmol) in absolute ethanol (20 mL) containing catalytic amounts of triethylamine (0.5 mL) and acetylacetone (0.15 mL, 1.5 mmol) was added to the reaction mixture, which was heated under reflux for 10 hours and then left to cool. The solid product was poured into water containing a few drops of hydrochloric acid, and the filtration and crystallized from ethanol collected the precipitate. Brown solid yielded: [(60%), mp 131–133°C; IR (v/cm⁻¹): 3415–3212 (OH, NH₂ and NH), 1690, 1672 (str. CO); ¹H NMR (δ, ppm): 0.88 (t, 3H, CH₃), 1.17–1.65 (s, 32H, CH₂ aliphatic), 3.89 (s, 3H, OCH₃), 5.31 (s, 1H, OH), 6.81 (s, 2H, NH₂), 7.26–7.59 (m, 8H, ArH and CH of pyridine ring), and 8.08 (s, 1H, NH). Anal. Calc. for C₄₂H₄₂N₂O₂: C, 74.86; H, 8.29; N, 8.23. Found: C, 74.33; H, 8.56; N, 8.48.

2.2 Preparation of Surface Active Agents

There was an addition of different moles of propylene oxide (3, 5 and 7 moles) to some of the synthesized compounds (0.1 mol) in each case, using KOH as the catalyst. The quantity of propylene oxide, which was allowed to react, and the average degree of propoxylation were measured through the increment in mass of the reaction mixture (the increase of the weight of the mixture after the addition of propylene oxide is the average amount of propoxylation). Normally, the addition of propylene oxide given to the mixture of propoxylated products and their structures was confirmed on the basis of IR and ¹H NMR spectra. IR-spectra revealed a broad band in the region of (3500–2500) cm⁻¹ (OH) and two other bands in the region of (1172–1022) and (960–900) cm⁻¹ for (C=O-C ether linkage) beside the original bands of these compounds. ¹H NMR-spectra showed the protons of the propoxy groups, which appeared as broad multiple signals in the region of (3.00–4.00) in addition to the other signals of these compounds.

2.3 Antimicrobial Activity

The cap-assay method, containing (g/L) peptone 6, meat extract 1.5, glucose 1 and agar 20, were used. The medium was sterilized and divided while hot (50–60°C) in 15 mL portions among sterile Petri dishes of 9 cm in diameter. One millilitre of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petri dish. Each of the tested compounds (0.5 g) was dissolved in 5 mL of dimethylformamide. An amount of 0.1 mL of test solution was placed on a Whatman paper disc of 9 mm diameter, and the solvent was left to evaporate. These saturated discs were carefully placed on the surface of the inoculated solid

---

R. E.-Sayed and I. Althagafi
J. Oleo Sci. 65, (2) 177-192 (2016)
medium; each Petri dish contained at least three discs. The Petri dishes were incubated at 5°C for an hour to permit good diffusion, transferred to an incubator of 85°C overnight and then examined. The results were recorded by measuring the inhibition zone diameters \( \gamma \), which were tabulated in Tables 2 and 3.

2.4 Determination of the Performance Properties of the Newly Synthesized Compounds

2.4.1 Surface and interfacial tension

Surface and interfacial tension measurements on (18–30) a-c were carried out according to Findlay\(^{33}\) with a Krüss tensiometer\(^{34}\) (Kruss GmbH, Hamburg, Instrument Nr. Kc) for different concentrations of the synthesized surfactants (0.05–10-6 mOL/L), using a platinum-iridium ring at constant temperature (25 ± 1°C). Paraffin oil was used for the interfacial tension measurements. The tensiometer was calibrated using the method described in ASTM Designation: D1331-01\(^{35}\).

2.4.2 Cloud point

By gradually heating a surfactant solution (1.0 wt%) in a temperature-controlled bath and recording the temperature when the clear or nearly clear solutions became definitely turbid, the cloud point was determined. The reproducibility of this temperature was checked by cooling the solutions until they became clear again\(^{36}\).

2.4.3 Wetting time

Determination of the wetting time was carried out by immersing a sample of cotton fabric in 1.0 wt% aqueous solution of surfactants\(^{30}\).

2.4.4 Foaming properties

A typical method was used in which 25 mL of the 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; then the foam height was measured\(^{40}\).

2.4.5 Emulsification stability

Emulsification stability was prepared from 10 mL of a 20 nmol aqueous solution of surfactant and 5 mL of toluene at 40°C. Emulsion stability was determined as the time that took 9 mL of aqueous layer to separate from the emulsion, counting since cession of shaking\(^{41}\).

2.5 Biodegradability

The biodegradation tests of the synthesized nonionic surfactants were performed according to the river water Die-Away method\(^{42}\). In this test, a stirred solution containing the tested surfactant (1,000 ppm) was incubated at 25°C. Samples were withdrawn daily, filtered using Whatman filter paper and the surface tension was measured using a Du Nouy tensiometer. The process was repeated for seven days. The biodegradation percentage D% was calculated in terms of the measured surface tension according to this Eq. \( D = [ ( \gamma_t - \gamma_0 ) / ( \gamma_0 - \gamma_0 ) ] \times 100 \), where \( \gamma_t \) = surface tension at time t, \( \gamma_0 \) = Surface tension at time zero (initial S.T.), \( \gamma_0 \) = Surface tension of the blank experiment at a time (t) (without sample).

3 RESULTS AND DISCUSSION

3.1 Synthesis

The purpose of this work is to synthesis, certain surface active agents containing heterocyclic nucleus for application as surface and pharmaceutical activities. Our approach to the synthesis of target molecules started from the condensation of 4-amino-acetophenone 1 with 4-hydroxy-3-methoxybenzaldehyde 2 by stirring in alkaline ethanolic solution to afford the chalcone derivative 3, which was stirred with stearoyl chloride\(^{43}\) in dry acetone containing a catalytic amount of triethyl amine and given the adduct 4. The ring closure reaction of 4 with malononitrile in the presence of ammonium acetate under reflux condition in ethanol for five hours gave N-(4-(6-amino-5-cyano-4-(4-hydroxy-3-methoxyphenyl) pyridin-2-yl) phenyl) stearamide 5. This reaction apparently involves an intra-molecular heterocyclization through an anticipated Michael-type addition\(^{44, 45}\) to give the final isolable product 5 (Scheme 1).

Poly-functionalized heterocyclic derivatives play a significant role in the drug industry\(^{46}\). Therefore, it is not surprising that synthesis of poly-functionalized heterocyclic derivatives has received important attention. In that bearing, β-enaminonitrile moiety in 5 was shown to be extremely reactive towards nitrogen nucleophiles. Thus, the reaction of 5 with malononitrile in ethanolic sodium ethoxide solution affords pyridine derivative 6. In the same manner, treatment of 5 with formamide in DMF with a few drops of piperidine furnished N-(4-(4-amino-5-(4-hydroxy-3-methoxyphenyl) pyrido[2,3-d]pyrimidin-7-yl) phenyl) stearamide 7 in a 73% yield (Scheme 2). In contrast, cyclocondensation of 5 with hot formic acid resulted in the formation of the pyrimidinone derivative 8 in 51% yields. Moreover, the reaction of 5 with hydroxylamine hydrochloride by heating under reflux in glacial acetic acid with anhydrous sodium acetate gave N-(4-(3-amino-4-(4-hydroxy-3-methoxyphenyl)-1H-pyrazolo[3,4-b] pyridin-6-yl) phenyl)stearamide 9.

An additional pathway for synthesis of pyrido[2,3-d] [1,3]thiazine derivative 10 was achieved through the reaction of 5 with carbon disulphide in pyridine (Scheme 3). Similar chemistry was involved in forming N-(4-(4-amino-5-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyrido [2,3-d]pyrimidin-7-yl)phenyl)stearamide 11 or N-(4-(4-amino-5-(4-hydroxy-3-methoxyphenyl)-2-thioxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)phenyl)stearamide 12 by heating under reflux of 5 with urea or thiourea in absolute ethanol in the presence of sodium ethoxide.

181

**J. Oleo Sci. 65, (2) 177-192 (2016)**
An extension of this work is for synthesis heterocyclic derivatives. Thus, heating of 5 with o-phenylenediamine or o-aminophenol in ethanol in the presence of piperidine for a long period gave the benzo[d]imidazole or oxazol derivatives 13 and 14, respectively. This reaction was proceeded by the initial addition of hydrogen to the cyano group, which then underwent intramolecular cyclization through loss of the NH3 molecule, leading to the formation of the final products 13 and 14, respectively.

Moreover, the reaction of 5 with ethylenediamine in the presence of a catalytic amount of carbon disulphide furnished N-(4-(6-amino-5-cyano-4-(4-hydroxy-3-methoxyphenyl)pyridin-2-yl)phenyl)stearamide 15. Furthermore, enamionitrile 5 was hydrolyzed with sulphuric acid on cold to give nicotinic acid derivative 16.

Finally, the reaction of 5 with acetyl acetone produced N-(4-(6-acetyl-5-amino-4-(4-hydroxy-3-methoxyphenyl)-7-methyl-1,8-naphthyridin-2-yl)phenyl)stearamide 17. The formation of 17 can be explained by condensation of acetyl acetone with an amino group in 5, followed by intramolecular cyclisation through the addition of an active methylene group to the cyano group, forming the final product 17.

3.2 Preparation of Surface Active Agents (18-30) a-c

The extensive importance of surface active agents in useful applications, and scientific interest in their nature
Synthesis of Biosignificant Heterocyclic Derivatives

and properties, have precipitated a wealth of published literature on the subject. Our research is designed to prepare new heterocyclic compounds as surface active agents. Thus, propoxylation of the synthesised compounds (5–17) with different quantities of propylene oxide (3, 5 and 7 moles), in the presence of KOH as a catalyst, produced nonionic surfactants (18–30) a–c. Table 1, shows the conditions of the propoxylation reaction about the degree of propoxylation (number of moles of propylene oxide, which added, n = 3, 5, 7 moles). Also, displays the temperature degree of this reaction for each compound which above its melting point. Moreover, this table, illustrations, the yield, color and shape of the resulting compounds with its number. Scheme 4 shows the propoxylation of compounds 8 and 17 as a general example.

3.3 Antimicrobial Evaluation

All the synthesized compounds (18–30) a–c were tested in vitro against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis, Bacillus cereus), Gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli, Enterobacter aerogenes), as well as fungi (Aspergillus niger, Penicillium italicum, Fusarium oxysporum). As shown in Tables 2 and 3, the antimicrobial effect of the tested compounds was estimated by measuring the zone diameters, and the results were compared with those of well-known drugs (sulphadiazine) as a standard. The results revealed that most of the tested compounds showed variable inhibitory effects on the growth of Gram-positive and Gram-negative bacterial strains, and also against the antifungal strains. The results revealed from Table 2 that some of the tested compounds showed antibacterial activity. However, concerning the activity against Gram-positive bacteria (Bacillus subtilis), compounds 22c, 26c, 28c and 29c revealed excellent activity, compounds 23b, 24c, 25c and 26b displayed good activity and compounds 18a, 19a, 19c and 21c presented moderate activity. On the other hand, the Gram-negative bacteria (Pseudomonas aeruginosa) exposed high responses to five of the prepared products. Compound 29c showed excellent antibacterial activity towards Enterobacter aerogenes. Regarding the data of antifungal activity in Table 3, compounds 22c and 26c indicated excellent activity against Aspergillus niger, whereas compounds 24b, 25b, 25c and 27c displayed good

J. Oleo Sci. 65, (2) 177-192 (2016)
activity. Moreover, the compound 29b presented good activity toward *Penicillium italicum*. In general, most of the tested compounds showed better activity against the Gram-positive rather than the Gram-negative bacteria.

### 3.4 Surface Active Agents

#### 3.4.1 Surface active properties

The surface active properties of the propoxylated compounds (18–30) a–c were evaluated in a neutral medium. The data obtained are outlined in **Table 4**.
### Table 2  Antibacterial activity of the prepared compounds.

| Sample | *Staphylococcus aureus* | *Bacillus subtilis* | *Bacillus cereus* | *Pseudomonas aurignosa* | *Escherichia coli* | *Enterobacter aerogenes* |
|--------|-------------------------|---------------------|-------------------|-------------------------|------------------|-------------------------|
| 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    | ++                      | +++                 | ++                | +++                     | +                | ++                      |
| 29a    | +                       | +                   | +                 | –                       | +                | +                       |
| 29b    | +                       | +                   | +                 | ++                      | +                | +                       |
| 29c    | ++                      | +++                 | ++                | ++                      | +                | +++                     |
| 30a    | +                       | +                   | +                 | –                       | –                | –                       |
| 30b    | ++                      | +                   | ++                | ++                      | +                | +                       |
| 30c    | ++                      | ++                  | ++                | ++                      | +                | ++                      |

+++ Highly sensitive (21–25 mm); ++ Fairly sensitive (16–20 mm); + Slightly sensitive (15–10 mm); – Not sensitive.
### Table 3  Antifungal activity of the prepared compounds.

| Sample | *Aspergillus niger* | *Penicillium italicum* | *Fusarium oxysporum* |
|--------|---------------------|-------------------------|----------------------|
| 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    | -                   | +                       | -                    |
| 29a    | -                   | +                       | -                    |
| 29b    | -                   | ++                      | +                    |
| 29c    | +                   | +                       | +                    |
| 30a    | +                   | -                       | -                    |
| 30b    | +                   | +                       | -                    |
| 30c    | +                   | -                       | +                    |
| Sulphadiazine | ++ | ++ | +++ |

+++ Highly sensitive (21–25 mm); ++ Fairly sensitive (16–20 mm); + Slightly sensitive (15–10 mm); – Not sensitive.
3.4.1.1 Surface and Interfacial Tensions

All the prepared compounds showed pronounced surface and interfacial tension. The values are closer to one another, since all compounds bear the same hydrophobic n-octadecyl chain, while the difference in both heterocyclic moieties and the number of the propylene oxide units was responsible for the slight differences in other surfaces. The results exposed that an increase in the propylene oxide units of the hydrophilic portion led to a clear increase in the surface tension. This phenomenon is related to the increased hydrophilicity decreasing the adsorption of the surfactants at the interface.

3.4.1.2 Cloud Point

Since water solubility of nonionic surfactants varies inversely with temperature, all synthesized compounds showed high cloud points, which gave a performance in hot water (73–95°C). This is a fact behind all synthesized compounds having a high commercial quality at room temperature. In addition, knowing the cloud point helps us to determine the storage stability, since storing at temperatures significantly higher than the cloud point may result in phase separation and instability. As outlined in Table 4, the cloud point for the synthesized surfactants augments by increasing the number of propylene oxide groups.

3.4.1.3 Wetting Time

Wetting time is the effectiveness of the surfactants as wetting agents, which evaluate a surfactant’s ability to transfer air from a weighted skein of cotton by spreading wetting. The results designated that these surfactants possess wetting power on cotton fabric substrates. Increasing the number of ethylene oxide units in the chain led to a decrease in wetting power because the surface tension increased accordingly; therefore, the surface free energy of these surfactants decreased.

3.4.1.4 Foaming Properties

Recent developments in the design of dyeing machines, such as more rapid circulation of liquor, can result in greater foam formation in the dye bath. This inconvenience has increased the importance of developing low-foaming dyeing auxiliaries. Table 4 presents the low-foaming properties of our surfactants. Each compound exhibited not only low foam production (measured by the height of foam initially produced) but also high-foaming stability (measured by the height of foam produced after five minutes). It appears that positioning the multiple hydrophilic groups at an internal position increases the area for every molecule, decreases the cohesive force at the surface and results in lower foaming efficiency. Generally, the foam height of the synthesized surfactant increases by augmenting the propylene oxide units for every surfactant molecule.

3.4.1.5 Emulsion Stability

Emulsification is an important property of surfactants that broadens their applications. Emulsification is an important property of surfactants that broadens their applications. For instance, tiny fragments of oil suspended in pure water will spontaneously assemble themselves into much larger mass. In the presence of an appropriate surfactant, the interfacial tension between the two immiscible liquids is reduced to a sufficiently low value; thus, emulsification takes place and permits stability of minute droplets of oil in the bulk of the water. The emulsifying power of the prepared surfactants, in terms of time needed for the separation of 9 mL of the solution, is presented in Table 4. The data show that the formed emulsion stability decreases as the number of propylene oxide units increases. Obviously, the surfactant’s solubility in the oil phase decreases as the hydrophilic part (n) increases, resulting in weaker emulsion. Generally, the measured time ranged between 45 and 70 minutes, thus indicating moderate emulsifying properties for the synthesized surfactants.

3.4.2 Biodegradability of the Synthesized Surfactants

Detergent surfactants represent one of the best investigated groups of chemicals in terms of their environmental fate and effects. To ensure the synthesized compounds are eco-friendly, the biodegradation Die-Away test in river water has been estimated and gave good to excellent results (Table 5). In the river Die-Away test, the amount of surfactant presented in river water was determined at certain time intervals. Measurements of surface tension or foaming properties could be used if no indication of the extent of degradation can be obtained for the compounds that have been lost. The results of biodegradation reflected that the biodegradability decreased by increasing the number of propylene oxide units. Moreover, the results showed that in the first day, 40–50% of the surfactants were biodegradable; after that, they decreased by 15–20% until the sixth or seventh day, and then they died away. This means these compounds are safe for human beings as well as environments, so they can be used in the manufacture of drugs, pesticides, emulsifiers, cosmetics, textiles and dyes, etc.

4 CONCLUSION

Our study was extended to the synthesis of surface active agents containing a heterocyclic and fused system. This study reports the successful synthesis of a new series of polyfunctional pyridine and fused pyridine derivatives linked to a fatty chain that exhibited good activities toward tested Gram-negative and Gram-positive bacteria and fungi. New classes of surface active agents were synthesized by subjecting the synthesized compounds to different quantities of propylene oxide. All the new surfactants displayed good surface active properties that the size of the hydrophilic part affects. The lower the number of propylene oxide units, the more effective is the surfactant in decreasing the surface and interfacial tension. In addition,
## Table 4  Surface properties of nonionic compounds.

| Compd  | n*  | Surface tension (mN/m) 0.1 wt% | Interfacial tension (mN/m) 0.1 wt% | Cloud point (°C) 1.0 wt% | Wetting time (sec) 0.1 wt% | Foam height (mm) 1.0 wt% | Emulsion stability (min) 20 mol |
|--------|-----|-------------------------------|-----------------------------------|--------------------------|----------------------------|---------------------------|-------------------------------|
| 18a    | 3   | 33                            | 9.0                               | 77                       | 65                         | 89                        | 70                            |
| 18b    | 5   | 35                            | 9.0                               | 79                       | 57                         | 116                       | 66                            |
| 18c    | 7   | 36                            | 9.5                               | 80                       | 55                         | 127                       | 61                            |
| 19a    | 3   | 36                            | 9.2                               | 81                       | 61                         | 78                        | 64                            |
| 19b    | 5   | 36                            | 9.7                               | 82                       | 58                         | 84                        | 59                            |
| 19c    | 7   | 37                            | 10.0                              | 90                       | 55                         | 100                       | 50                            |
| 20a    | 3   | 35                            | 9.1                               | 78                       | 69                         | 84                        | 69                            |
| 20b    | 5   | 38                            | 10.3                              | 78                       | 67                         | 98                        | 64                            |
| 20c    | 7   | 39                            | 10.7                              | 81                       | 64                         | 115                       | 58                            |
| 21a    | 3   | 31                            | 8.7                               | 80                       | 88                         | 75                        | 67                            |
| 21b    | 5   | 35                            | 9.0                               | 82                       | 85                         | 87                        | 65                            |
| 21c    | 7   | 37                            | 10.2                              | 88                       | 84                         | 99                        | 60                            |
| 22a    | 3   | 30                            | 8.7                               | 79                       | 65                         | 81                        | 62                            |
| 22b    | 5   | 31                            | 8.9                               | 80                       | 61                         | 92                        | 57                            |
| 22c    | 7   | 35                            | 9.4                               | 87                       | 57                         | 112                       | 51                            |
| 23a    | 3   | 33                            | 9.1                               | 75                       | 70                         | 107                       | 58                            |
| 23b    | 5   | 34                            | 9.2                               | 78                       | 66                         | 121                       | 55                            |
| 23c    | 7   | 35                            | 9.3                               | 85                       | 62                         | 128                       | 48                            |
| 24a    | 3   | 29                            | 8.5                               | 78                       | 62                         | 100                       | 56                            |
| 24b    | 5   | 30                            | 8.8                               | 80                       | 60                         | 111                       | 54                            |
| 24c    | 7   | 33                            | 9.1                               | 89                       | 52                         | 128                       | 47                            |
| 25a    | 3   | 29                            | 8.6                               | 85                       | 64                         | 96                        | 55                            |
| 25b    | 5   | 30                            | 8.7                               | 88                       | 63                         | 108                       | 51                            |
| 25c    | 7   | 34                            | 9.0                               | 95                       | 56                         | 125                       | 45                            |
| 26a    | 3   | 38                            | 10.4                              | 83                       | 69                         | 115                       | 67                            |
| 26b    | 5   | 39                            | 10.7                              | 86                       | 68                         | 126                       | 64                            |
| 26c    | 7   | 41                            | 11.1                              | 93                       | 61                         | 135                       | 57                            |
| 27a    | 3   | 37                            | 10.3                              | 76                       | 67                         | 109                       | 70                            |
| 27b    | 5   | 39                            | 10.5                              | 78                       | 66                         | 114                       | 66                            |
| 27c    | 7   | 42                            | 11.2                              | 97                       | 59                         | 123                       | 60                            |
| 28a    | 3   | 30                            | 8.5                               | 76                       | 58                         | 100                       | 60                            |
| 28b    | 5   | 33                            | 9.1                               | 79                       | 55                         | 111                       | 56                            |
| 28c    | 7   | 38                            | 10.2                              | 87                       | 47                         | 126                       | 49                            |
| 29a    | 3   | 31                            | 8.6                               | 70                       | 52                         | 112                       | 70                            |
| 29b    | 5   | 34                            | 9.3                               | 73                       | 50                         | 121                       | 68                            |
| 29c    | 7   | 37                            | 10.2                              | 81                       | 45                         | 134                       | 65                            |
| 30a    | 3   | 33                            | 8.5                               | 78                       | 61                         | 99                        | 67                            |
| 30b    | 5   | 35                            | 9.4                               | 83                       | 59                         | 116                       | 65                            |
| 30c    | 7   | 38                            | 10.1                              | 91                       | 55                         | 128                       | 60                            |

n* No. of moles of propylene oxide. Error was: Surface and interfacial tensions = ± 0.1; Cloud point = ± 1°C; foam height = ± 2 mm; Wetting time = ± 1 sec; emulsion = ± 1 min.
Table 5  Biodegradability of the prepared surfactants.

| Compds. | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day |
|---------|---------|---------|---------|---------|---------|---------|---------|
| 18a     | 45      | 58      | 72      | 79      | 88      | 95      |         |
| 18b     | 44      | 56      | 69      | 78      | 86      | 92      |         |
| 18c     | 41      | 50      | 62      | 70      | 80      | 90      |         |
| 19a     | 48      | 59      | 70      | 82      | 91      | -       | -       |
| 19b     | 47      | 58      | 69      | 78      | 86      | 93      |         |
| 19c     | 46      | 55      | 68      | 75      | 82      | 91      |         |
| 20a     | 51      | 64      | 70      | 79      | 87      | 94      |         |
| 20b     | 49      | 57      | 69      | 77      | 85      | 91      |         |
| 20c     | 46      | 55      | 65      | 73      | 82      | 90      |         |
| 21a     | 49      | 63      | 71      | 80      | 92      | -       | -       |
| 21b     | 45      | 56      | 67      | 76      | 87      | 93      |         |
| 21c     | 42      | 53      | 66      | 74      | 86      | 92      |         |
| 22a     | 44      | 55      | 68      | 79      | 88      | 94      |         |
| 22b     | 40      | 53      | 67      | 76      | 87      | 94      |         |
| 22c     | 40      | 52      | 65      | 71      | 83      | 90      |         |
| 23a     | 45      | 61      | 70      | 78      | 92      | -       | -       |
| 23b     | 45      | 56      | 65      | 75      | 86      | 95      |         |
| 23c     | 44      | 53      | 61      | 70      | 83      | 90      |         |
| 24a     | 43      | 57      | 69      | 79      | 90      | -       | -       |
| 24b     | 40      | 53      | 64      | 76      | 85      | -       | -       |
| 24c     | 38      | 52      | 61      | 70      | 82      | 93      |         |
| 25a     | 43      | 59      | 69      | 80      | 93      | -       | -       |
| 25b     | 40      | 55      | 63      | 75      | 87      | 92      |         |
| 25c     | 39      | 52      | 62      | 72      | 87      | 91      |         |
| 26a     | 51      | 62      | 71      | 79      | 91      | 93      |         |
| 26b     | 50      | 62      | 70      | 78      | 89      | 90      |         |
| 26c     | 50      | 61      | 68      | 75      | 83      | 91      |         |
| 27a     | 55      | 62      | 72      | 83      | 92      | -       | -       |
| 27b     | 50      | 59      | 68      | 80      | 89      | 94      |         |
| 27c     | 48      | 59      | 67      | 75      | 84      | 91      |         |
| 28a     | 51      | 60      | 71      | 84      | 95      | -       | -       |
| 28b     | 45      | 55      | 67      | 79      | 89      | -       | -       |
| 28c     | 41      | 53      | 63      | 72      | 84      | 93      |         |
| 29a     | 50      | 62      | 70      | 82      | 91      | -       | -       |
| 29b     | 44      | 59      | 69      | 82      | 90      | -       | -       |
| 29c     | 43      | 57      | 65      | 76      | 88      | 93      |         |
| 30a     | 45      | 56      | 69      | 83      | 94      | -       | -       |
| 30b     | 43      | 51      | 65      | 82      | 91      | -       | -       |
| 30c     | 42      | 50      | 63      | 77      | 89      | 94      |         |

Error of calculations was: Biodegradation rate = \( \pm 0.5 \% \)
the synthesized surfactants showed good degradation susceptibility within seven days. Consequently, the synthesized compounds and surfactants are safe for human beings as well as the environment. They can be used in the manufacture of drugs, cosmetics, moderate emulsifiers, wetting agents, textiles and dyes.

ACKNOWLEDGEMENT

The authors would like to thank the staff of the Microbiology Department, Faculty of Science, Umm Al-Qura University for biological activity screening of the tested compounds.

REFERENCES

1) Liu, Y.; Ai, K.; Lu, L. Polydopamine and its derivative materials: Synthesis and promising applications in energy, environmental, and biomedical fields. Chem. Rev. 114, 5057-5115 (2014).
2) Ariga, K.; Yamauchi, Y.; Rydzek, G.; Ji, Q.; Yonamene, Y.; Wu, K. C.-W.; Hill, J. P. Layer-by-layer Nanoarchitectonics: Invention, Innovation, and Evolution. Chem. Lett. 43, 36-68 (2014).
3) Chandrani, C.; Frances, P.; Ayusman, S. Chemical conversion pathways for carbohydrates. Green Chem. 17, 40-71 (2015).
4) Sharma, S.; Kaur, S.; Bansal, T.; Gaba, J. Review on Synthesis of Bioactive Pyrazoline Derivatives. Chem. Sci. Trans. 3, 861-875 (2014).
5) Siham, A. R. Synthesis of a New Series of Pyridine and Fused Pyridine Derivatives. Molecules 17, 10902-10915 (2012).
6) Patel, N. B.; Agrapat, S. N.; Shaikh, F. M. Synthesis and antimicrobial activity of new pyridine derivatives-I. Med. Chem. Res. 20, 1033-1041 (2011).
7) Patel, N. B.; Agrapat, S. N. Synthesis and antimicrobial studies of new pyridine derivatives. Chem. Heterocycl. Compd. 45, 1343-1353 (2009).
8) Srivastava, A.; Pandeya, S. N. "Indole" a versatile nucleus in pharmaceutical field. Int. J. Curr. Pharm. Res. Rev. Res. 4, 5-8 (2011).
9) Paronikyan, E. G.; Noravany, A. S.; Dzhagatspany, I. A.; Nazaryan, I. M.; Paronikyan, R. G. Synthesis and antiviral activity of isoazolo-[5,4-b]-pyrano(thiopyrano)-[4,3-d]-pyridine and isoazolo[4,5-b]-2,7-naphthyridine derivatives. Pharm. Chem. J. 36, 465-467 (2002).
10) Bernardino, A. M. R.; De Azevedo, A. R.; Pinheiro, L. C. D.; Borges, J. C.; Carvalho, V. L.; Miranda, M. D.; De Meneses, M. D. F.; Nascimento, M.; Ferreira, D.; Rebelo, M. A. Syntehsis and antiviral activity of new 4-(phenylamino)/4-[methylidin]-2-ylamino]-1-phenyl-1H-pyrazolo[3,4-b]-pyridine-4-carboxylic acid derivatives. Med. Chem. Res. 16, 352-369 (2007).
11) Tucker, T. J.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M.; Liang, Y.; McGaughey, G.; Liu, M. Discovery of 3-[6-(Amino-1H-pyrazolo-[3,4-b]-pyridine-3-yl)methoxy]-2-chlorophenoxy]-5-chlorobenzonitrile (MK-4965): A potent, orally bioavailable HIV-1 non-nucleoside reverse transcriptase inhibitor with improved potency against key mutant viruses. J. Med. Chem. 51, 6503-6511 (2008).
12) Mamolo, M. G.; Zampieri, D.; Falagiani, V.; Vio, L.; Ferreglia, M.; Ferrone, M.; Prici, S.;Banfi, E.; Scialino, G. Antifungal and antinocytobacterial activity of new N1-[1-aryl-2-(1Himidazol-1-yl) and 1H-1,2,4-triazol-1-yl]-ethylidene]pyridine-2-carboxamidrazone derivatives: A combined experimental and computational approach. ARKIVOC (v)231-250 (2004).
13) Geffen, D.; Soliman, R.; Soliman, F. S. G.; Abdel-Khalek, M. M.; Issa, D. A. E. Synthesis of new series of pyrazolo[4,3-d]pyrimidin-7-one and pyrido[2,3-d]pyrimidin-4-ones for their bacterial and cyclin-dependent kinases (CDKs) inhibitory activities. J. Med. Chem. 40, 408-420 (2011).
14) Golubev, A. S.; Starostin, G. S.; Gunkhik, K. S.; Perregudov, A. S.; Rodygin, K. C.; Rubtsova, S. A.; Slepkikhin, P. A.; Kuchin, A. V.; Chkamokov, N. D. Synthesis of new fluorine-containing pyrazolo-[3,4-b]-pyridinones as promising drug precursors. Russ. Chem. Bull. 60, 733-745 (2011).
15) De Clercq, E. Recent highlights in the development of new antiviral drugs. Curr. Opin. Microbiol. 8, 552-560 (2005).
16) Tariq, E. S. A. Synthesis of some novel pyrazolo-[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidin derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents. Eur. J. Med. Chem. 44, 4385-4392 (2009).
17) Tollefson, M. B.; Acker, B. A.; Jacobsen, E. J.; Hughes, R. O.; Walker, J. K.; Fox, D. N. A.; Palmer, M. J.; Freeman, S. K.; Yu, Y. 1-(2-Ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidines as potent phosphodiesterase 5 (PDE5) inhibitors. Bioorg. Med. Chem. Lett. 20, 3120-3124 (2010).
18) Rajesh, K.; Yogesh, C. Synthesis, antimicrobial and antiviral activities of novel 1H-1,4-diazepine containing pyrazolopyrimidinone moiety. J. Chem. Sci. 121, 497-502 (2009).
19) Ivachtchenko, A. V.; Dmitriev, D. E.; Golovina, E. S.; Dubrovskaya, E. S.; Kadayeva, M. G.; Koryakova, A. G.; Kysil, V. M.; Mitkin, O. D.; Tkachenko, S. E.; Okun, I. M.; Vorobiov, A. A. Synthesis of cycloalkane-annelated 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines and their
Synthesis of Biosignificant Heterocyclic Derivatives

J. Oleo Sci. 65, (2) 177-192 (2016)

Matthew, D. H. Recent Strategies for the Synthesis of Pyridine Derivatives. Chem. Eur. J. 16, 12052-12062 (2010).

20) Himani, V.; Aiman, A.; Rauf, A.; Pohad, M. H.; Iqbal, A. Synthesis and antimicrobial evaluation of fatty chain substituted 2,5-dimethyl pyrrole and 1,3-benzoxazin-4-one derivatives. J. Saud. Chem. Soc. (2014) doi: 10.1016/j.jscs.2014.04.008.

22) Khairujjaman, L.; Aiman, A.; Rauf, A. Synthesis and spectral characterization of novel fatty acid chain substituted pyrazole derivatives. Rasayan J. Chem. 7, 276-280 (2014).

23) Yildirim, A.; Cetin, M. Synthesis and Characterization of Some Novel Higher C,N-Diphenyl Nitrones, Isoxazolines, and Mercaptobenzimidazoles as Oleochemicals. Phosphorus Sulfur Silicon Relat. Elem. 187, 952-964 (2012).

24) Yildirim, A.; Ozturk, S.; Cetin, M. Long-Chain Alkylthia-Benimidazoles as Corrosion Inhibitors for Carbon Steel in H2SO4 Solution. Phosphorus Sulfur Silicon Relat. Elem. 188, 855-863 (2013).

25) Wang, L.; Li, C.; Wang, N.; Li, K.; Chen, X.; Yu, X.Q. Enzyme-mediated domino synthesis of 2-alkylbenzimidazoles in solvent-free system: A green route to heterocyclic compound. J. Mol. Catal. B: Enzym. 67, 16-20 (2010).

26) Mukhopadhyay, C.; Ghosh, S.; Sengupta, S.; Soumis, C. Enzyme-mediated synthesis of 2-alkyl substituted under microwave irradiation: Anti-proliferative effect of some representative compounds on human histiocytic lymphoma. RSC Adv. 1, 1033-1037 (2011).

27) Yadav, S.; Kumar, P.; Clercq, E. D.; Balzarini, J.; Pannecouque, C.; Dewan, S. K.; Narsaminha, B. 4-(1-(substituted aryl/alkyl carbonyl)-benzimidazol-2-yl)-benzenesulfonic acids: Synthesis, antimicrobial activity, QSAR studies, and antiviral evaluation. Eur. J. Med. Chem. 45, 5985-5997 (2010).

28) Lishuai, J.; Weihtong, Q.; Limei, L.; Huan, P. Design and Surface/Interface Properties of Asymmetric Triazine Carboxyl Betaine Surfactants. J. Surf. Deterg. 17, 629-636 (2014).

29) Laurier, L. S.; Elaine, N. S.; Marangoni, D. G. Surfactants and their applications. Annu. Rep. Prog. Chem., Sect. C. 99, 3-48 (2003).

30) El-Sayed, R. Synthesis and Heteroaannulation of Pyridine and Related Heterocyclic Systems Having Surface and Biological Activities. J. Oleo Sci. 64, 761-774 (2015).

31) El-Sayed, R.; Saleh, A. A. Synthesis of Some New Thiazole, Oxazole, Pyrimidine and Pyridazine Derivatives from 2-cyano-N-octadecyl-acetamide as Antimicrobial and Surface Active Agents. J. Heterocyclic Chem. (2015). 19 Jan (2015). DOI: 10.1002/jhet. 2288.

32) El-Sayed, R.; Ashgar, B. H. Synthesis of various nitrogen heterocycles as antimicrobial surface agents. J. Heterocyclic Chem. 51, 1245-1251 (2014).

33) Morgós, J.; Sallay, P.; Farkas, L.; Rusznák, I. A new approach of ethoxylation catalyzed by bridge head nitrogen containing compounds. J. Am. Oil Chem. Soc. 63, 1209-1210 (1986).

34) Abou-Zeid, A. A.; Shehata, Y. M. A simple technique for assaying antibiotics using methylene blue as an indicator. Ind. J. Pharmacy 31, 72-75 (1969).

35) Findly, A. Practical Physical Chemistry 6th Ed. Longmans London, pp. 1040-1069 (1963).

36) Weil, J. K.; Stirton, A. J.; Nunez-Ponzoa, M. V. Ether alcohol sulfates. The effect of oxypropylation and oxybutylation on surface active properties. J. Am. Oil Soc. 43, 603-609 (1966).

37) ASTM D1331-01. Standard Test method for surface and interfacial tension of solutions of surface active agents. (2001).

38) Draves, C. Z.; Clarkson, R. A new method for the evaluation of wetting agents. J. Am. Dye Stuff Report 20, 201 (1931).

39) Durham, K. Properties of detergent solutions-amphiplathy and adsorption, Vol 1. Surf Activity Deterg. MacMillan & Co. Ltd., London, p. 1 (1961).

40) Ross, J.; Milles, G. D. Apparatus for comparison of foaming properties of soaps and detergents. Oil Soap 18, 99-102 (1941).

41) Scholnick, F.; Linfield, W. M. Lactose-derived surfactants (III): fatty esters of oxy-alkylated lactitol. J. Am. Oil Chem. Soc. 54, 430-435 (1977).

42) Falbe, J. Surfactants for consumer, Springer Verlag, Heidelberg, Chap. 4 (1986).

43) Amine, M. S.; Eissa, A. M. F.; El-Sawy, A. A.; Shaaban, A. F. El-Sayed, R. New heterocycles having a double character as antimicrobial and surface active agents. Part1: nonionic compounds from fatty acid isothiocyanate. Ind. J. Chem. 44B, 1724-1730 (2005).

44) Figueras, J. 3-Aryl-1,2-dihydroquinazolines. J. Org. Chem. 31, 803-806 (1966).

45) Ayman, W. E.; Sherif, M. S.; Nadia, R. M. Heterocyclic synthesis with activated nitriles: an expeditus synthetic approach of polyfunctionally substituted pyrroles, heterocyclo-pyrimidines and coumarins. ARKIVOC (x) 85-94 (2001).

46) Aly, A. A.; Iman, A. G. Facile Synthesis of New Pyrazolo-pyrimidine Derivatives of Potential Biosignifcant Interest. J. Kor. Chem. Soc. 55, 781-786 (2011).

47) El-Sayed, R.; Khairou, K. S. Propoxylated Fatty Thiazole, Pyrazole, Triazole, and Pyrrole Derivatives with Antimicrobial and Surface Activity. J. Surf. Deterg. 18, 661-673 (2015).

48) Naveen, K.; Rashmi, T. Synthesis and surface studies
of anionic gemini surfactant in the different counterions. Int. J. Ind. Chem. 6, 59-66 (2015).

49) Iman, A. G.; Mahasen, S. A.; Amal, A. M.; Alaa, S. G. Fatty Acids in Heterocyclic Synthesis. Part XIV: Synthesis of Surface Active Agents from Some Novel Class of Oxadiazole, Thiadiazole and Triazole Derivatives Having Microbiological Activities. J. Surf. Deterg. 17, 509-523 (2014).

50) Bajpai, D.; Tyagi, V. K. Fatty Imidazolines: Chemistry, Synthesis, Properties and Their Industrial Applications. J. Oleo Sci. 55, 319-329 (2006).