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Fadhil Lafta Faraj, Salih Mahdi Salman and Tammar Hussein Ali

New Surface Active and Biological Active Compounds with Heterocyclic Core

Fadhil Lafta Faraj[1], *Salih Mahdi Salman[2,a)] and Tammar Hussein Ali [3]

[1]*Departments of Chemistry, College of Sciences, University of Diyala, Republic of Iraq*
[2]*Department of Chemistry, College of Medicine, University of Diyala, Republic of Iraq*
[3]*Department of pharmaceutical chemistry, Faculty of Pharmacy, Al-Muthanna University, Al Muthanna , Iraq.*

[a)] **Corresponding author: waamrs@yahoo.com, +964-7719608316*

ABSTRACT. Series of new compounds have been synthesized via coupling of heterocyclic compound with different halides alkyl chain length (C10-C18). The precursor of synthesis got from phenyl hydrzinhydrochloride in three steps. The first is the reaction with isoproylmethyl ketone in acetic acid to yield (2, 3, 3-trimethyl-3H-indole) using Fischer reaction. The second is treatment of the later with POCl3 in DMF through Vilsmeier-Haack reaction to produce 2-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde. Finally, the reaction with 2-aminophenol in glacial acetic acid to produce the precursor (2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal. Five ether derivatives build from this compound by Williamson reaction using (C10-C18) alkyl halides in present of potassium carbonate. The structure and purity of the synthesized compound was confirmed by spectroscopy methods including IR techniques, both 1H, 13C NMR spectroscopy in addition to CHN analysis. The biological activity and surface tension properties of those compounds were investigated and most of them show compatibility with the aim of the synthesis**.**

KEYWORDS: Fischer reaction, Vilsmeier-Haack reaction, Williamson reaction, biological activity and surface active compounds.

INTRODUCTION

Heterocyclic chemistry is part of organic chemistry study synthesis and the physiochemical properties of heterocyclic molecules and investigate the important applications for them in different fields of the life.[1-3] The availability of natural raw material and chemical process that can be applicable in this branch of chemistry opens the sky for chemist and scientists to use those raw material and chemical process in modification some known compounds or synthesis new chemicals with multiple purposes.[4-8] Heterocyclic compounds classified probably as the biggest brand in organic compounds.[9, 10] A good example of such those compounds [3], which pass through some synthetics modification and transformation to produce useful derivatives. This compound was subjected to coupling with aniline and many substituted aniline to yield two new series shows cytotoxicity against breast cancer cell line AMJ13.[11] .Another series derived from this compounds show a good results against lymphatic cell in metaphase in human blood.[12] In the current study we would like to enhanced the properties of this heterocyclic compound through synthesis new series by coupling with haled alkyl with different chain length via Williamson reaction aiming to get amphiphilic structures with both biological activity and surface active properties.

MATERIAL AND METHODS:

Materials

Chemicals were furnished by Fisher scientific, Fluka, Merck and Aldrich suppliers $POCl_3$, DMF, DMSO, NaOH, $CDCl_3$, Na_2SO_4, potassium carbonate, Phenyl hydrzinhydrochloride, isoproylmethylketone acetic acid, 2-

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aminophenol, and sodium acetate. They were used as received without further purification. The melting points of the target surfactants were measured by open capillary melting point apparatus without further corrections.

Instruments

The IR spectroscopy was recorded by a Perkin-Elmer Spectrum 400 ATR-FT-IR spectrometer. 1H and ^{13}C NMR spectroscopy were done by using AVN Bruker 400 and 600MHz FT NMR spectrometer and JEOL Lambda 400 MHz FT-NMR spectrometer. Tetramethylsilane TMS was used as internal standard. Deuterated 1,4-dioxane-*d8* CD_2Cl_2 were used as solvents. Elemental analysis was performed using Perkin Elmer CHNS/O 2400 series II elemental analyzer.

Synthesis of 2,3,3-trimethyl-3H-indole [1].

A mixture of phenyl hydrzinhydrochloride and isoproylmethyl ketone (1mmole from each), and (0.5 mmole) of acetic acid was refluxed with (5 ml) 0f ethanol for 2 hours at 117 ºC with continuous stirring. The mixture was cooled down after TLC indicates the end of the reaction. NaOH (1M) was added for neutralization of the solution and diluted with about (100ml) of water. After three times extraction with (50 ml) $CDCl_3$, then Na_2SO_4 applied for drying. The solvent was evaporated by available means and the yield subjected to purification to produce pure brown oily indolenines [1] in 90% yield.[13-16]

Synthesis of 2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde [2].

The Vilsmeier reaction was applied to synthesis this compound by adding $POCl_3$ (60 mmole, 6Ml) drop by drop to about (30 Ml) of DMF with cooling and contentious stirring for about 20 minutes at 0 °C. Compound [1] dissolved in (10 Ml) DMF and added to the later solution with heating to about 75°C and stirring for nearly 6 hours. After the reaction solution cool down by addition of crushed ice, (3g) of sodium acetate added with stirring. Compound [**2]** crystals were formed and separated by filtration after 24 hours from the end of the reaction.[17, 18]

Synthesis of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal [3].

2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde [**2]** (1.075 g, 5 mmol) **and** (0.546 g, 5 mmol) of 2-aminophenol in distilled ethanol (60 mL) and (3 mL) glacial acetic acid was added was refluxed in water a bath at 75ºC for 5 h. The solvent was reduced and left over night at room temperature. Two days later, the brown crystals of compound 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal [**3]** were collected. Yield is : 1.4g 92%.[12]

General Procedure Of Williamson Etherification

A solution of (0.150g, 0.500 mmol) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal [3] dissolved in (10 mL) DMF, then, was added (0.28g, 2.00 mmol) of potassium carbonate. The mixture was stirring for 20 min, after that (0.500 mmol) of corresponding alkyl halide poured to the solution and reflux 2 h at 85°C in water bath. After 4h the reaction TLC was indicating to the end of reaction, the crude was extracted by chloroform and water, evaporates the organic layer then, added (10 mL) of ethyl alcohol, and left outside. Yellow crystals had been seen the next day, filtered off, washed by ethyl alcohol and dried using silica-gel. [19-21]

Synthesis of 3-(2-decyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [4]

A solution of (0.150g,) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** was reacted with (0.112 g) of decane bromide according to the Williamson general synthesis procedure to yield (170g, 77%) of compound **[4].** Anal calcd. For $C_{29}H_{38}N_2O_2$ (446.62): C, 77.99; H, 8.58; N, 6.27, Found: C, 78.03; H, 8.65; N 6.30. IR data (cm-1): 3046 υ(N-H), 2965 υ(C-H aromatic), 2868 υ(C-H aliphatic), 1664 υ(O=CH), 1612 υ(C=C), 1586 υ(C=NH), 1446 υ(CH_2), 1240 υ(C-N), 1165 υ(C-O) and 738 υ(C-H bending) .^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.06(d, 1H, *J* = 12.20Hz, N*H*), 9.76(s, 1H, C*H*O), 8.46(d, 1H, *J* = 12.20Hz, C*H*=N), 7.50(d, 1H, Ar-H), 7.42(d, 1H, Ar-*H*), 7.31(t, 2H, Ar-*H*), 7.23(d, 1H, Ar-H), 7.18(t, 1H, Ar-H), 7.03(m, 2H, Ar-H), 4.17(t, 2H, α-CH_2), 2.04(cinq, 2H, *β*-CH_2),1.67(s, 6H, 2x CH_3), 1.56(cinq, 2H, γ-CH_2), 1.24(bulk, 12H, CH_2) and 0.89(t, 3H, CH_3).
^{13}C and APT NMR (100 MHz, DMSO-d_6) *δ* (ppm): 187.44ppm (O=C*H*), 183.11ppm (Ar-NH*C*=C), 151.98, 149.36, 145.78 and 129.40 (*Ar*-H), 127.32 (*C*H=N), 125.85, 125.85, 124.83, 120.95, 118.56, 115.58, 112.57 and 115.58 (*Ar*-H), 108.44ppm (*C*-C=O 69.14ppm (CH_3*C*-CH_3), 53.78, 31.87, 29.54, 29.29, 26.07 and 23.67 ppm(CH_2), 22.67 ppm (2x *C*H_3 indole ring) and 14.11(CH_3).

Synthesis of 3-(2-dodecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [5]

A solution of (0.150g) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** was reacted with (0.125g) of dodecane bromide bromide according to the Williamson general synthesis procedure to produce

(190g, 83%) of compound **[5].** Anal. calcd. For $C_{31}H_{42}N_2O_2$ (474.68): C, 78.44; H, 8.92; N, 5.57 Found: C, 78.50; H, 9.05 ; N 5.60. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 13.96 (d, 1H, N*H*), 9.67(s, 1H, C*H*O), 8.36(s, 1H, C*H*=N), 7.41(d, 1H, Ar-*H*), 7.23(d, 1H, Ar-*H*), 7.21(d, 2H, Ar-*H*), 7.12(m, 2H, Ar-*H*), 6.94(m, 2H, Ar-*H*), 4.08(t, 2H, α-CH_2), 1.95(cinq, 2H, *β*-CH_2),1.57(s, 6H, 2x CH_3), 1.16(bulk, 18H, CH_2) and 0.79(t, 3H, CH_3).

Synthesis of 3-(2-tetradecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [6]

A solution of (0.150g) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** was reacted with (0.139g) of tetradecan bromide bromide according to the Williamson general synthesis procedure to give (0.200g, 80%) of compound **[6].** Anal calcd. For $C_{33}H_{46}N_2O_2$ (502.73): C, 78.84; H, 9.22; N, 5.57. Found: C, 78.80; H, 9.27; N 5.61. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 13.94 (d, 1H, N*H*), 9.66(s, 1H, C*H*O), 8.36(s, 1H, C*H*=N), 7.41(d, 1H, Ar-*H*), 7.23(d, 1H, Ar-*H*), 7.21(d, 2H, Ar-*H*), 7.13(t, 1H, Ar-*H*), 7.08(d, 1H, Ar-*H*), 6.94(m, 2H, Ar-*H*), 4.07(t, 2H, α-CH_2), 1.94(cinq, 2H, *β*-CH_2),1.57(s, 6H, 2x CH_3), 1.46 (cinq, 2H, γ-CH_2), 1.19(bulk, 20H, CH_2) and 0.78(t, 3H, CH_3).

Synthesis of 3-(2-hexadecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [7]

A solution of (0.150g) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** was reacted with (0.153g) of hexadecan bromide bromide according to the Williamson general synthesis procedure to yield (0.22g, 85%) of compound **[7].** Anal calcd. For $C_{35}H_{50}N_2O_2$ (530.78): C, 79.20; H, 9.49; N, 5.28. Found: C, 79.16; H, 9.60; N 5.32. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 13.96 (d, 1H, *J* = 11.10Hz, N*H*), 9.66(s, 1H, C*H*O), 8.36(d, 1H, *J* = 11.10Hz, C*H*=N), 7.42(d, 1H, Ar-*H*), 7.33(d, 1H, Ar-*H*), 7.20(d, 2H, Ar-*H*), 7.12(t, 1H, Ar-*H*), 7.08(d, 1H, Ar-*H*), 6.92(m, 2H, Ar-*H*), 4.08(t, 2H, α-CH_2), 1.93(cinq, 2H, *β*-CH_2),1.44(s, 6H, 2x CH_3), 1.27 (cinq, 2H, γ-CH_2), 1.17(bulk, 24H, CH_2) and 0.79(t, 3H, CH_3). ^{13}C and APT NMR (100 MHz, DMSO-d_6) *δ* (ppm): 187.45ppm (O=*C*H), 183.10 ppm (Ar-NH*C*=C), 151.96, 149.37, 145.77 and 129.40 (*Ar*-H), 127.32 (*C*H=N), 125.86, 125.86, 124.83, 120.95, 118.56, 115.58, 112.57 and 115.58 (*Ar*-H), 108.44ppm (*C*-C=O 69.15ppm (CH_3*C*-CH_3), 53.47, 31.93, 29.54, 29.06, 26.06 and 23.67 ppm(CH_2), 22.70 ppm (2x *C*H_3 indole ring) and 14.13(CH_3).

Synthesis of 3-(2-octadecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [8]

A solution of (0.150g) of 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** was reacted with (0.167 g) octadecan bromide bromide according to the Williamson general synthesis procedure to yield (0.24g, 89%). Anal calcd. For $C_{37}H_{54}N_2O_2$ (558.84): C, 79.52; H, 9.74; N, 5.01. Found: C, 79.47; H, 9.85; N 4.90. ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 14.06(d, 1H, *J* = 11.01Hz, N*H*), 9.76(s, 1H, C*H*O), 8.46(d, 1H, *J* = 11.01Hz, C*H*=N), 7.50(d, 1H, Ar-*H*), 7.32(d, 1H, Ar-*H*), 7.21(d, 2H, Ar-*H*), 7.04(d, 1H, Ar-*H*), 7.03(t, 1H, Ar-*H*), 7.01(m, 2H, Ar-*H*), 4.17(t, 2H, α-CH_2), 2.04(cinq, 2H, *β*-CH_2),1.66(s, 6H, 2x CH_3), 1.55 (cinq, 2H, γ-CH_2), 1.28(bulk, 28H, CH_2) and 0.90(t, 3H, CH_3).

General Methods For Biological Activity Measurements

A Kirby-Bauer disc diffusion method was applied to measure the biological activity for this series of compounds using Mueller-Hinton agar. Ampicillin used as standard bioactive agent for bacteria, while Amphotericin B was used as standard for fungi. DMSO solvent was used as a negative control.[22-26] (For more details see the supplementary file)

Critical Micelle Concentration (CMC)

KSV Sigma tensiometer was used to measure the critical micelle concentration (CMC) based on DuNouy methods.[27] (For more detail see supplementary files)

Emulsifying Test

Emulsifying test was done the methods suggested by Yokoyama and et al using special formula containing methyl laurate and the surfactants.[28] (For more details see supplementary file)

RESULTS AND DISCUSSIONS

Synthesis

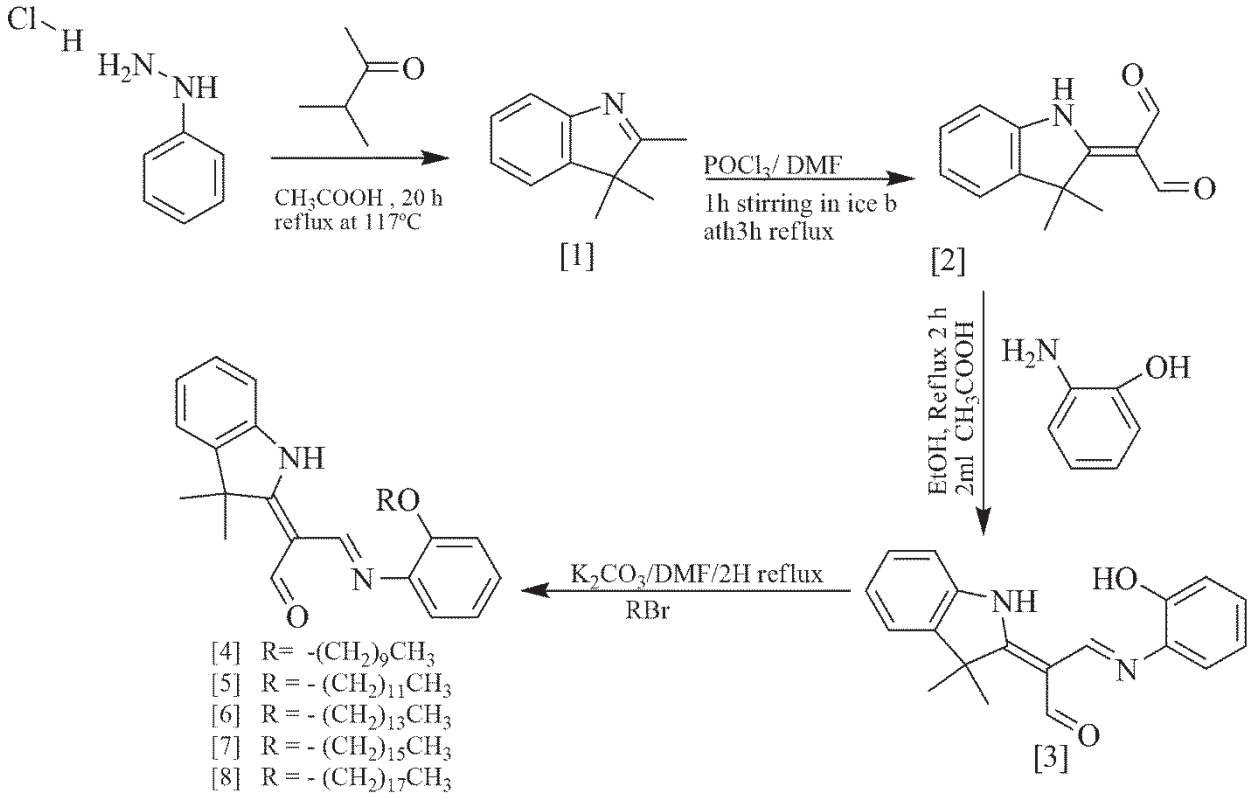

FIGURE 1. Synthetic scheme of the new series

Synthetic scheme of the final product are shown in figure 1 step by step. The synthesis started from the reaction between Phenyl hydrzinhydrochloride and isoproylmethyl ketone in present of acetic acid to get 2, 3, 3-trimethyl-3H-indole **[1]** via Fischer reaction. The later was treated with $POCl_3$ in DMF via Vilsmeier-Haack reaction to produce 2-(3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde **[2]**, which easily converted to the precursor 2-(3,3-dimethylindolin-2-ylidene)-3-(2-hydroxyphenylimino) propanal **[3]** by the reaction with 2-aminophenol in present of glacial acetic acid. New series of five ether derivatives build from this precursor by Williamson reaction with four alkyl halide (C_{10}, C_{12}, C_{16}, C_{18}) in present of potassium carbonate. The structure and purity of those four synthesized compound is confirmed by CHN analysis and spectroscopy. The hygroscopic properties of the synthesized derivatives and limitation of instruments led to some deviation in hydrogen element calculations in elemental analysis. While both carbon and nitrogen shows acceptable value in comparing with the theoretical calculations.

IR spectrum was run for compound **[4]** which is show the absorptions of (N-H) 3046 cm^- ,(C-H) aromatic at 2965 cm^{-1}, (C-H) aliphatic 2868 cm^{-1}, (O=CH) at 1664 cm^{-1}, (C=C) at 1612 cm^{-1}, (C=NH) at 1586 cm^{-1}, (CH_2)1446 cm^{-1}, (C-N) at 1240 cm^{-1}, (C-O) at 1165 cm^{-1} and (C-H bending) at 738 cm^{-1}. ^{1}H NMR spectrums (figure 2) for the synthesized compounds show a doublet at δ =14.06 for 1H of (N*H*), singlet at δ =9. 76 for 1H of (C*H*O), doublet at δ= 8.46 for 1H of (C*H*=N), doublet at δ= 7.50 for (1H, Ar-H), doublet at δ =(7.32-7.42) for 1H of (Ar-*H*),triplet at δ= 7.31 for 2H of (Ar-*H*), doublet at δ =(7.21-7.23) for 1H of (Ar-H), triplet at δ =(7.04-7.18) for 1H of (Ar-H), multiplet at δ= 7.03 for 2H of (Ar-H), triplet at δ=4.17 for 2H of (α-CH_2), cinq. at δ =2.04 for 2H of (*β*-CH_2), singlet at δ =(1.66-1.67) for 6H (2x CH_3), cinq. at δ =(1.55-1.56) for 2H of (γ-CH_2),bulk at δ =(1.24-1.28) for 12H (CH_2) and triplet at δ =(0.89-0.90) for 3H of (CH_3).

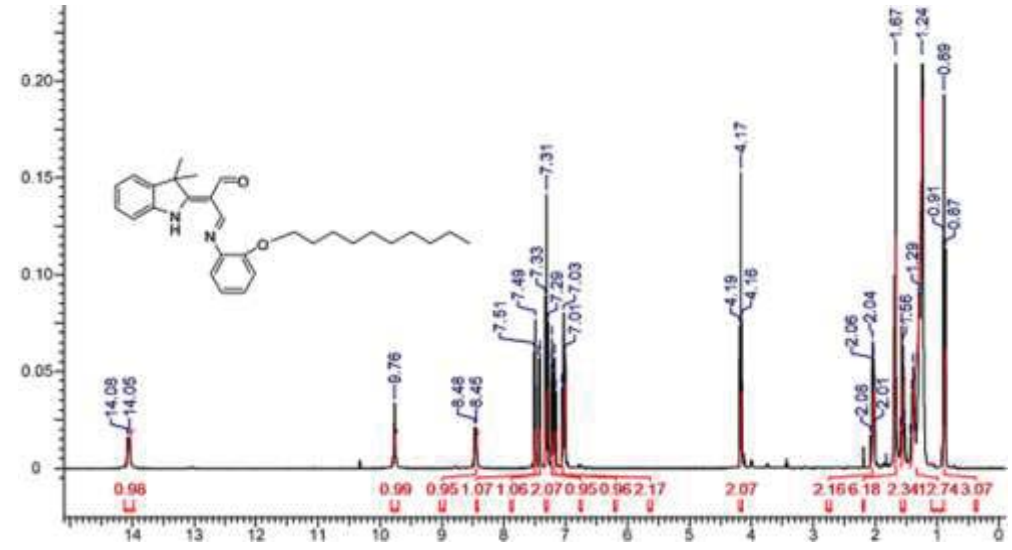

FIGURE 2. [1]H NMR for3-(2-decyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [4]

[13]C NMR spectrums support the formation the mentioned compounds since they are show peak at 187.44ppm assigned carbonyl carbon (O=*C*H), peak at 183.11ppm attributed (Ar-NH*C*=C),while the four peaks between 151.98-129.40 is assigned to (*Ar*-H), peak at 127.32 for (*C*H=N),and the eight peaks in between 125.85- 115.58 are belong to (*Ar*-H), the peak at 108.44ppm (*C*-C=O , another one at 69.14ppm for (CH_3*C*-CH_3), and the bulk is located between 53.78-23.67 ppm(CH_2), the peak of the two methyl attached to indole ring is at finally the terminal methyl is at 14.11(CH_3).(for more detail about NMR spectrum .(see supplementary material for more data about NMR analysis or the other synthesized compounds)

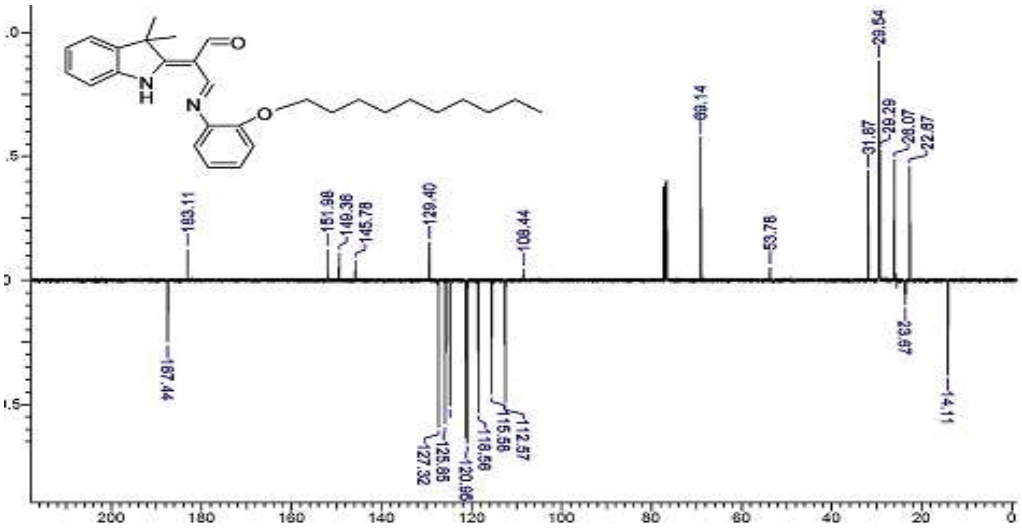

FIGURE 3. [13] C NMR for3-(2-decyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde [4]

Biological Activity

The bioactivity for all the target synthesized derivatives were investigated contra Gram-positive bacteria (Bacillus subtilis, Bacillus cereus) and Gram-negative bacteria (Pseudomonas aurignosa, Enterobacter aerogenes), in addition to two fungi (Penicillium italicum, Fusarium oxysporum). Table (1) shows the outcome of this investigation, which

is exhibit an excellent activity for 3-(2-decyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde **[4]** and 3-(2-dodecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde **[5]** especially toward Bacillus cereus, Enterobacter Aerogenes and Fusarium oxysporum. While the other compounds 3-(2-tetradecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde **[6],** 2-hexadecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde **[7]** and 3-(2-octadecyloxy-phenylimino)-2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-propionaldehyde **[8]** exhibit low activity the for two reasons. The first reason reducing the accessibility to critical regions of the bacteria and fungi by the later compounds due to the shielding that may happen because of the long alkyl group, While the second reason may belong to the poor solubility of this compound in water at room temperate due to the hydrophilic- hydrophobic imbalance because of containing too long alkyl group comparing to the hydrophilic polar group. The result for compound **[4&5]** is still compatible with the biological activity of the other heterocyclic compound.[29-31]

TABLE 1. Biological activity measurements for the synthesized compounds

	Sample	Gram positive bacteria		Gram negative bacteria		Fungi	
		Bacillus Subtilis	Bacillus Cereus	Pseudomonas Augenosa	Enterobacter Aerogenes	Penicillium Italicum	Fusarium Oxysporum
Standard	Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0
	Ampicillin Antibacterial	18	17.3	21	22	11	12.5
	Amphotericin B Antifungal	9.3	13	16	17.2	18	20
Experimental	[4]	9	17	11	20	11	20
	[5]	7.7	13	9	15	9	15
	[6]	7	9	7.5	10	7.5	10
	[7]	6	8	7	9.4	7	8.4
	[8]	6	7	6	8	7	7.5

Surface Active Properties

The synthesized compounds exhibit moderate solubility in water at 25 ºC and relatively high Krafft temperature. Water solubility and the value of krafft temperature reflect the degree of the high interaction between the synthesized compounds molecules through hydrogen bonding. This is the main reason for the relatively high Krafft temperature for compounds of the new series. The Krafft temperature for surfactants compounds **[4-7]** increased by increasing the number of the carbon atoms in the alkyl groups as shown in table 2. This behavior and demonstrate the increasing of the hydrophobicity.

The critical micelle concentrations (CMC) listed in table (2) was measured by DuNouy ring based on surface tension calculation, which was carried out for the series of the target compound solutions with different concentrations. The surface tensions and CMC values for this series are about (29-33 mN/m at CMC 0.5 mmol/L. Those values are compatible with previously reported value of the heterocyclic containing surfactants.[30]

TABLE 2. Physical and emulsions properties of the synthesized compounds

Com. No.	Chain Length	CMC investigation			Mp °C	Phase separation time
		CMC mmol /L	Surface tension mN/m	T_k° C		
[4]	C10	29	0.6	25	126-127	2 days
[5]	C12	30	0.55	28	134-136	3 days
[6]	C14	31	0.50	32	140-142	7 days
[7]	C16	33	0.46	39	146-148	< a month
[8]	C18	35	0.52	45	153-155	< a month

To evaluate emulsions properties test was done according to procedures suggested by Yokoyama and et al in 2001. The results were listed in table (2) which indicate to very good separation times for the long alkyl group surfactants [C_{16} and C_{18}], Both stay for more than a month without phase separation, while the shorter alkyl groups [C_{10}, C_{12}, C_{14}] show separation period within a week. The emulsion transformed a gel after about 21 days, which to heat for about 40 ºC to back to liquid again.

CONCLUSION

It can be concluding that the new compound with heterocyclic core containing long alkyl group chain show both biological active against some kind of bacteria and fungi in addition to ability for reducing the surface tension of water. Those two properties make the target compounds useful for pharmaceutical and industrial applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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