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ORIGINAL ARTICLE

Synthesis and Biologically Activity of Novel 2- Chloro -3-Formyl -1,5-Naphthyridine Chalcone Derivatives

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KEYWORDS

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ABSTRACT: A new and efficient procedure has been described for the synthesis of 2- chloro-1,5-Naphthyridine-3-carbaldehyde(1) from the condensation of N-(pyridine-3-yl) acetamide in presence of dimethylformamide and phosphorous oxychloride through Vilsmeir – Haack cyclization. The condensation of compound (1) with acetophenone, p-hydroxy acetophenone, pyridine-3-acetyl, furan-2-acetyl, and indole-2-acetyl in the presence of ethanolic sodium hydroxide through Claisen- Schmidt condensation give quinolinyl chalcones (2a-e) and it's further treated with dimethyl sulfoxide in the presence of iodine to obtained iodo chalcone compounds (3a-e). The smooth and selective bromination of chalcones (2a-e) affords dibromide compounds (4a-e). The structure of prepared compounds was identification by spectral and physical methods. Synthesized compounds (4a, 3e, 3b and 4e) give good biological activity from against Staphylococcus aureus and Staphylococcus epidermidis and moderate activity against *Escherichia Coli* and Proteus Vulgaris.

INTRODUCTION

Naphthyridine compounds are naturally occurring and have an important biological and pharmacological activity. They are indispensable for the metabolism of all microorganisms and living cells which are widely distributed in nature and are essential to life [1, 2]. Recently heterocyclic compounds including naphthyridine moiety have been synthesis and reported as having potent pharmaceuticals and have excellent biological activity [3]. Now a day, the quinoline derivatives are used as starting materials for the preparation of various fused naphthyridine [4, 5].

The hetero Diels-Alder reaction has been used to prepare heterocyclic compounds as the most efficient and powerful method [6, 7]. And some transition metal salt such as copper and indium trichloride is used as a catalyst in the Diels-Alder reaction [8]. The addition reaction is used to prepare 1,5-naphthyridine from the reaction of 3-amino pyridine, aldehyde, and alkene or alkyne using $BF_3.OEt_2$ as a lewis acid [9,10]. A light and effective method for the synthesis of chromino naphthyridine derivatives using domino reaction of 3-amino pyridine and o-propargylated salicylaldehyde using copper in indium trichloride as a catalyst [11]. A series of 1,5-naphthyridine has been prepared by a Suzuki cross-coupling [12], chalcones and their derivatives have been synthesized by Claisen – Schmidt condensation is also medically important and possesses antimalarial, antibacterial, and antifungal properties[13,14]. Also, recently some naphthairidine compounds were studied as drug compounds against the emerging coronavirus, theoretically, using the Docking program [15].

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MATERIALS AND METHODS

Instrumentation

M.P. was measured on electrothermal CIA9300 M.P. apparatus and is uncorrected. Proton NMR spectra were acquired at 25^{o}C on a 400MHz spectrometer (Bruker using Dimethylsulfoxide-d$_6$ as solvent). IR (KBr, cm^{-1}) spectra were obtained on Bruker – Tensor27 spectrometer.

Synthesis of 2-chloro-1,5-naphthyridine-3-formaldehyde (1)[16].

A 3-(N-pyridine-3-yl) acetamide (5 mmoles) in (15 mmoles) of dry dry formamide, (60 mmoles) of phosphorus oxychloride was added drop-wise. Then refluxed the reaction mixture for 16 hrs. with continuous stirring, then poured into crushed ice-cold water and precipitated solid was formed, filtered, washed with cold water, and recrystallized from ethanol to give yellow powder as a powder (yield 55%, m.p. 141-144^{O}C). Fourier-transform infrared (KBr cm^{-1}), 1672(C=O), 1568(C=N), 750(C-Cl), 2780 (C-H). While ^{1}H-NMR(400 M.Hertz, Dimethylsulfoxide-d$_6$, δ, ppm),6.99-7.02(t,1H,H-7),7.19-7.22(t,1H,H-6), 7.33-7.34(d,1H,H-8), 7.64-7.65(d,1H,H-4), 9.84(s,1H,CHO). ^{13}CNMR (400 M.Hertz, Dimethylsulfoxide-d$_6$, δ, ppm), 128.23(C$_8$), 133.70(C$_7$), 134.21(C$_9$), 135.31(C$_{10}$), 126.51(C$_3$), 136.1(C$_6$), 145.23(C$_4$), 150.19(C$_2$), 189.30(CHO).

General procedure for preparation of quinolinyl – chalcones(2a-e)[17]

A equimolar mixture of 2-chloro -3-for my-1,5-naphthyridine (1) (5mmoles) and different ketones (acetophenone , p-hydroxy acetophenone , pyridine-3-acetyl, furan-2-acetyl and indole-2-acetyl) (5 mmoles) in ethanol medium (15 ml) in the presence of aqueous solution of sodium hydroxide (40%, 3 mmoles, 3 ml) is stirred continuously for 6 hrs at room temperature . Then the mixture was kept overnight at 25^{o}C and poured into 200 ml cold water and acidified with dilute (HCl), the crestal yield was separated, filtered, dried, and recrystallized by ethanol.

Compound(2a)

E-3-(2-chloro-1,5-naphthyridine-3-yl)-1-(4-phenyl)prop-2-ene-1-one) : (Yield 75%, m.p. : 167-170^{o}C), Fourier-transform infrared (KBr cm^{-1}), 1669 cm^{-1}(C=O),1580 cm^{-1}(C=C), 1565 cm^{-1}(C=N), 760 cm^{-1}(C-Cl), ^{1}HNMR (400 M.Hertz, Dimethylsulfoxide-d$_{6,}$ δ, ppm), 7.61-7.63(d,4H,H-4, H-6, H-7, H-8), 7.44-7.52(s,5H, benzene ring), 6.54-6.56(d,1H,Hα), 5.86(d,1H,Hβ).

Compound(2b)

E-3-(2-chloro-1,5-naphthyridine-3-yl)-1-(4-hydroxy phenyl) prop-2-ene-1-one): (Yield 80%, m.p. 187-189^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1680 cm^{-1} (C=O), 1601 cm^{-1} (C=C), 1565 cm^{-1} (C=N), 755 cm^{-1}(C-Cl), 3435(OH), ^{1}HNMR(400 M.Hertz, Dimethylsulfoxide-d6, δ, ppm), 10.14 (s,1H,OH), 8.23(s,1H,H-4), 7.13-7.15(d,1H,H-), 7.33-7.36(t,1H,H-7), 7.86-7.88(d,1H,Hα), 7.50-7.65(m,4H,ArH), 8.68(d,1H,H-6), 8.70(d,1H,H-8).

Compound(2c)

E-3-(2-chloro-1,5-naphthyridine-3-yl)-1-(pyridine-3-yl)prop-2-ene-1-one): (Yield 65%, m.p. 260-262^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1675 cm^{-1} (C=O), 1615 cm^{-1} (C=C), 1575 cm^{-1} (C=N), 750 cm^{-1} (C-Cl), ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d$_6$, δ, ppm), 8.13(s,1H,H-4), 7.48-7.24(s,4H, H pyridine), 7.781-7.74(d,1H,H-6), 7.32-7.35(t,1H,H-7), 7.52 (d,1H,Hα), 8.04-7.98(d,1H,H-8), 6.94 (t,1H,Hβ).

Compound(2d)

E-(3-(2-chloro-1,5-naphthyridine-3-yl)-1-(furan-2-yl)prop-2-ene-1-one): (Yield 70%, m.p. 180-182^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1669 cm^{-1} (C=O), 1595 cm^{-1} (C=C), 1565 cm^{-1} (C=N), 750 cm^{-1} (C-Cl), ^{1}HNMR (400 M.Hertz, Dimethylsulfoxide-d$_6$, δ, ppm), 8.72(s,1H,H-4), 7.68(d,1H,H-8), 8.00-8.06(d,1H,Hα), 7.66-7.7(d,1H,H-6), 7.99-7.94(d,1H,Hβ), 7.62-7.65(t,1H,H-7), 8.13-8.15(m,3H, furan).

Compound(2e)

E-(3-(2-chloro-1,5-naphthyridine-3-yl)-1-(1H-idol-3-yl) prop-2-ene-1-one)**:** (Yield 70%, m.p. 256-258^{o}C, Fourier-transform infrared (KBr cm^{-1}) 1663 cm^{-1} (C=O), 1605cm^{-1} (C=C), 1545cm^{-1} (C=N), 745cm^{-1} (C-Cl), ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 9.84(s,1H,NH), 8.00(s,1H,H-4), 7.26-7.28(d,1H,H-8), 7.33-7.36(d,1H,H-7), 7.98-7.97(t,1H,H-6), 7.19-7.23(d,1H,H-α), 6.85-6.86(d,1H,H-□), 7.27-7.31(m,5H,indole).

General Procedure for preparation of iodo chalcones (3a-e) [18].

To a solution (3mmoles) of chalcones(2a-e) was added (15ml)of DMSO. To the above mixture (1-2)crystal of iodine was added and the reaction mixture was acidified by adding 2 drops of sulfuric acid. The mixture was heated under refluxed for 3 hrs, then ice-cold water was added with stirring for 1 hr, the precipice solid was formed, filtered, washed with (5%)solution of sodium thiosulphate and finally with (25ml) cold water, and recrystallized from ethanol gave the title compounds(3a-e).

Compound (3a)

2Z-1-(2-phenyl)-3-(2-chloro-1,5-naphthyridine-3-yl)-3-iodoprop-2-ene-1-one: (Yield 55%, m.p. 221-223^{o}C), Fourier-transform infrared (KBr γ cm^{-1}) 1665 cm^{-1} (C=O), 1485 (C=C), 1570 (C=N), 750 (C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 7.92(s,1H, Hα), 7.50-7.40(s & d ,4H,H-4 ,H-6, H-8, H-7), 7.29-7.24(m,5H,Ar-H).

Compound (3b)

2Z-1-(p-hydroxyphenyl)-3-(2-chloro-1,5-naphthyridine-3-yl)-3-iodoprop-2-ene-1-one: (Yield 65%, m.p. 235-237^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1670 cm^{-1} (C=O), 3455(OH), 1495(C=C), 1560(C=N), 750(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 9.09(s,1H,OH), 7.99(s,1H,Hα), 7.61(s,1H,H-4), 7.66(d,1H,H-6), 7.41(d, H,H-8), 7.35(t,1H,H-7), 7.78,7.72-7.09,6.98(d,d,4H,Ar-H).

Compound (3c)

2Z-1-(pyridine-3-yl)-3-(2-chloro-1,5-naphthyridine-3-yl)-3-iodoprop-2-ene-1-one: (Yield 60%, m.p. 242-245^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1675 cm^{-1} (C=O), 1495(C=C), 1582(C=N), 755(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 8.10(s,1H,H-4), 7.56(d,1H,H-8), 7.88(d,1H,C6pyridine), 7.99(d,1H,C5 pyridine), 7.88(d,1H,H-6), 7.61(t,1H,H-7), 7.31-7.19(m,1H,C4 pyridine), 7.08(t,1H,C3 pyridine), 7.72(s,1H, Hα).

Compound (3d)

2Z-1-(furan-2-yl)-3-(2-chloro-1,5-naphthyridine-3-yl)-3-iodoprop-2-ene-1-one: (Yield 65%, m.p. 256-258^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1667 cm^{-1} (C=O), 1501(C=C), 1565(C=N), 750(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 8.12(s,1H,Hα), 8.08(s,1H,H-4), 7.91(d,1H,H-6), 8.03(d,1H,H-8), 7.78(t,1H,H-7), 6.53-6,57(m,1H,H-2 furan), 6.97(d,1H,H-3 furan), 7.39 (d,1H,H-3 furan) .

Compound (3e)

2Z-1-(H-indol-3-yl)-3-(2-chloro-1,5-naphthyridine-3-yl)-3-iodoprop-2-ene-1-one: (Yield 70%, m.p. 265-267^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1670 cm^{-1} (C=O), 1490(C=C), 1585(C=N), 755(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 10.02(s,1H,NH), 7.96(s,1H,H-4), 7.79-7.70 (d,1H,H-8), 7.65-7.60(m,1H,H-7), 7.86(d,1H,H-6), 7.21-6.28(m,5H, indole), 7.92(s,1H,Hα).

Synthesis of dibromide (4a-e) [19]

General procedure

To a solution of (3mmoles) of (2a-e) in 15ml of dry dichloromethane in an ice bath, cooled to (0^{o}C) was added dropwise over a half-hour, the (0.1 ml) of bromine with mixture pliable to stand overnight with stirring. The yield was reduced to half by the evaporator. The products are purified by recrystallization from chloroform to obtain pure compounds.

Compound (4a)

2,3-dibromo-1-phenyl -3-(2-chloro-1,5-naphthyridine) propane-1-one: (Yield 65%, m.p. 145-147^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1695 cm^{-1} (C=O), 1565(C=N), 3055(Ar-H). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm): 8.28(s,1H,H-4), 8.14-

7.92(d,1H,H-6), 7.80-7.68(d,1H,H-8), 7.40(t,1H,H-7), 4.58(d,1H,CH_2Br), 4.43(d,1H,C_3HBr), 7.27-6.81(m,5H,ArH).

Compound (4b)

2,3-dibromo-1-(p-hydroxyphenyl)-3-(2-chloro-1,5-naphthyridine) propane-1-one**:** **(**Yield 65%, m.p. 165-167^{o}C), Fourier-transform infrared (KBr ν cm^{-1}) 1691cm^{-1} (C=O), 1563(C=N), 3058(Ar-H). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 10.39(s,1H,OH), 8.51-8.39(s,1H,H-4), 7.95-7.70(d,1H,H-6),7.62-7.53(d,1H,H-8), 7.46-7.31(t,1H,H-7), 4.11(d,1H,C_2HBr), 3.37(d,1H,C_3HBr), 8.28-8.09,7.15-6.78(d.d,4H,ArH).

Compound (4c)

2,3-dibromo-1-(pyridine-3-yl)-3-(2-chloro-1,5-naphthyridine) propane-1-one: (Yield 45%, m.p. 195-198^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1683 cm^{-1} (C=O), 1560(C=N), 755(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 7.42(s,1H,H-4), 7.40-7.37(d,1H,H-8), 7.52-7.44(d,1H,C6 ,C2 pyridine), 7.21-7.17(d,1H,H-6), 7.13-7.09(t,1H,H-7),), 7.09-7.05(m,1H,C3, C5 pyridine), 4.90-4.70(d,1H,C_2HBr), 3.18-3.06(d,1H,C_3HBr).

Compound (4d)

2,3-dibromo-1-(furan-2-yl)-3-(2-chloro-1,5-naphthyridine) propane-1-one**:** **(**Yield 65%, m.p. 172-175^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1693 cm^{-1} (C=O), 1660(C=N), 755(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm): 7.71(s,1H,H-4), 7.52-7.48(d,1H,H-6), 7.34-7.31(d,1H,H-8), 7.28-7.25(t,1H,H-7), 7.23-7.21(m,1H,C2furan), 6.73(d,1H,C3furan), 6.71(d,1H,C4furan), 4.78(d,1H,C2HBr), 3.74-3.66(d,1H,C3HBr).

Compound (e)

2,3-dibromo-1-(1H-indol-3-yl) -3- (2-chloro-1,5-naphthyridine propane-1-one: (Yield 55%, m.p. 268-267^{o}C), Fourier-transform infrared (KBr cm^{-1}) 1680 cm^{-1} (C=O), 1585(C=N), 750(C-Cl). ^{1}HNMR (400 Mega Hertz, Dimethylsulfoxide-d_6, δ, ppm), 10.39(s,1H,NH), 8.08(s,1H,H-4), 8.00-7.90(d,1H,H-8), 7.85-7.50(m,1H,H-7), 7.44-7.41(d,1H,H-6), 8.21-8.12,6.92-6.68(d.d ,5H,indole), 4.16-4.56(d,1H,C_2HBr), 3.14(d,1H,C_3HBr).

RESULTS AND DISCUSSION

Many methods have been used to synthesize 1,5-naphthyridine [20, 21]. But the Vilsmeier method is found to be the most efficient method.

The mechanism includes the electrophilic compensation of the activated aromatic heterocyclic ring with halomethylene iminium salt, and then the iminium species converted into a many compounds of Novel heterocyclic systems. The starting compounds 2-chloro-1,5-naphthyridine-3-carbaldehyde were prepared from reaction of N-(pyridine-3-yl) acetamide with vilsmeier reagent at (80-90^{o}C). The cyclization of N-pyridyl acetamide was occur by adding drops from $POCl_3$ to dimethylformamide at (0-5^{o}C) then heated to 90^{o}C, (Figure 1).

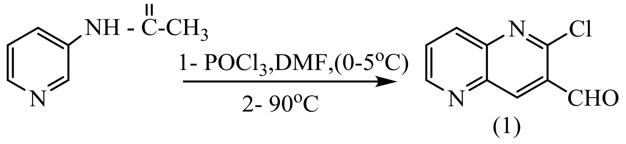

Figure 1. Cyclization of N-Pyridyl acetamide to 2-chloro-3-formyl-1,5-naphthyridine

The structure of starting compound (1) could agree with their spectral data. The Infra-Red spectra of these compounds showed many bands strong and sharp absorption at 1686 cm^{-1} for the (C=O) group and 1571 cm^{-1} for the imine group. The ^{1}H NMR spectra for these compounds in Dimethylsulfoxide-d_6 showed singlet at (9.84 ppm) for the proton of aldehyde. The ^{13}C NMR spectra showed a carbonyl peak at 192.25 ppm. The chalcones (2a-e) have been synthesized via Claisen-Schmidt condensation in ethanolic sodium hydroxide of 2-chloro -3-formyl-1,5-naphthyridine with acetophenone, p-hydroxy acetophenone, pyridine-3-acetyl, indole-2-acetyl & furan-2-acetyl to obtain α,β -unsaturated carbonyl compounds (Figure 2).

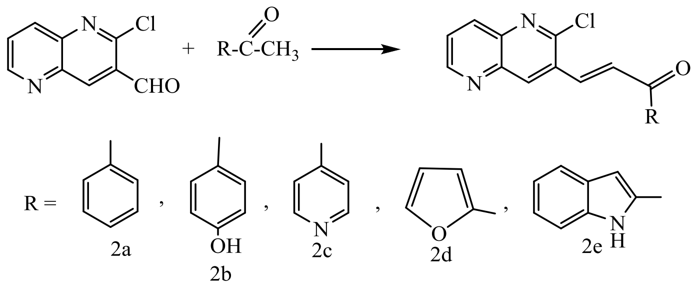

Figure 2. Synthesis of α, β -unsaturated carbonyl compounds

The Infra-Red Spectra of compounds(2a-e) showed characteristic absorption band at region(1653-1680)cm^{-1}for (C=O)group and at region(1545-1575 cm^{-1}) for imine group band shown at (3350 cm^{-1})due to OH group in compound(2b). The ^{1}HNMR spectra for compounds(2a-e) showed two peak doublet at the region(7.86-6.54ppm) and the region (7.13-5.85 ppm) due to the proton α and proton respectively for α,β -unsaturated carbonyl group, while the singlet peak appears at (10.14 ppm) due proton of the (OH)group for compound 2b).

The dimethyl sulfoxide in iodine is used as the oxidizing agent and functions as an iodinating agent for α,β -unsaturated ketones. The reaction was carried out by adding 1,2 crystals of iodine to the solution of chalcones (3a-e)in dimethyl sulfoxide then acidified by adding two drops of sulfuric acid, then refluxed the reaction mixture for one hour was achieved (Figure 3).

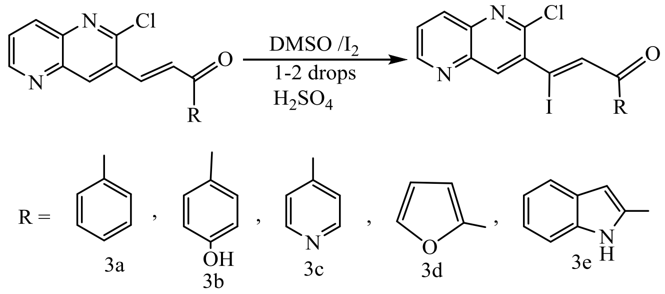

Figure 3. An iodinating agent for α, β -unsaturated carbonyl compounds

The IR spectra of compounds (3a-e) showed characteristic absorption band at region (1664-1675) cm^{-1}for (C=O) group and at region (1565-1585 cm^{-1}) for (C=N) group and absorption at (3455cm^{-1}) for (OH) group. The ^{1}HNMR spectrum for compound (3b) showed a singlet band at (9.09 ppm) for the proton of (OH) group for compound (3b) and another singlet at (7.99 ppm) for the proton of hydrogen attached to the ethanolic linkage of compound (3b). Smooth and selective bromination of chalcones compounds (2a-e) afforded good yield to the corresponding dibromide compounds (4a-e), The reaction is carried out by adding (0.1 ml) of bromine to α,β -unsaturated ketones in dry methane dichloride with cooled in an ice bath under stirring, thus compounds (4a-e) were obtained in good yields (Figure 4).

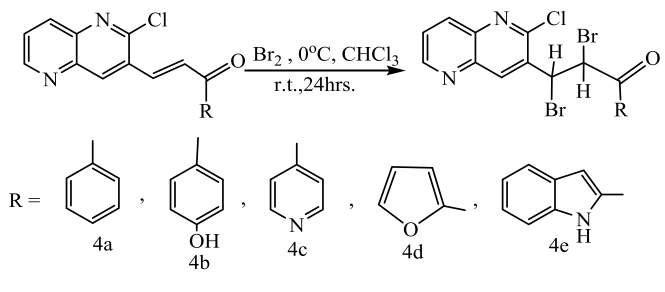

Figure 4. bromination of α,β -unsaturated carbonyl compounds.

The IR spectra of compounds (4a-e) showed absorption between the range (1680-1695) $cm^{-1}$for (C=O) group and at (3325 cm^{-1}) for OH group due to the compounds (4b). The ^{1}HNMR spectra for compounds (4a-c) showed two peak doublet at the region (4.54-4.11ppm) and the region (4.43-3.17 ppm) due to the proton of CH_2Br and CH_3Br and showed a single peak at (10.39 ppm) for (OH) in compound (4b).

Biological studies

The new compounds (2b, 2e, 3b, 3e, 4a and 4e) were screened antibacterial activity (grame positive and grame negative bacteria). The antibacterial test was carried out by disc – diffusion method [22, 23]. Ciprofloxacin was used as slandered for comparation by gauging the diameter of the inhibition zone at the end of (24hrs.) at 37°C. All the compounds were found to show strong activity against grame-positive bacteria and moderate activity against grame-negative bacteria. The result and listed in the Table1.

Table1. Antibacterial activity data for some selected compounds.

Compounds No.	**Compounds zone of inhibition / mm**			
	Staphylococcus aureus	***Staphylococcus epidermidis***	***E. Coli***	**Proteus Vagaries**
2b	16	15	10	10
2e	18	16	10	9
3b	24	19	12	12
3e	22	18	14	12
4a	21	19	17	14
4e	25	22	18	16
Control Ciprofloxacin mg disc^{-1}	19	18	16	14

CONCLUSIONS

In this synthetic work compound (1) was synthesized by Vilsmeier-Hack cyclization then converted to a different α, -unsaturated carbonyl compounds and characterized by spectral data. The compounds (2b, 2e, 3b, 3e, 4a and 4e) showed good activity against staphylococcus aureus and staphylococcus epidermis and moderate activity against grame negative bacteria such as *E. coli* and proteus vagaries.

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