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Synthesis Biological Studies of Some New Heterocyclic Compound Derived From 2-Chloro-3-Formyl Quinoline And 4-(Benzyl Sulfonyl) Acetophenone

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Abstract

A new series of quinoline chalcones have been prepared from condensations of 2-chloro-3-formyl quinoline (1) with 4-(benzothio) acetophenone(2) and 4-(benzyl sulfonyl) acetophenone(3). The reaction of chalcones(4,5) with bromine gives dibromide(6,7). New pyrazoline derivatives were synthesized by condensation of chalcones (4 or 5) with hydrazine hydrate to give (8,9) and with hydrazine hydrate in glacial acetic acid(gla) to give (10,11) and with phenyl hydrazine to give (12,13). The prepared chalcones (4,5) and dibromide(6,7) and pyrazoline derivative (8-13)have been screened for anti-bacterial activities against two gram positive *staphylococcus aureus* and *staphylococcus epidermidis* and two gram negative *Escherichia coli* and *Proteus vulgaris*. The synthesized compounds are proven by IR & NMR spectral and physical method.

Keywords: 2-chloro-3-formyl quinoline, Chalcones, Dibromide, 4-(benzyl sulfonyl) acetophenone, 4-(benzothio) acetophenone .

1. Introduction

Quinoline is class of nitrogen heterocyclic, which are a part of large number of natural and synthetic compounds which play important roles in may biological system and medical chemistry [1,2]. The quinoline skeleton is often used to design of many synthetic compounds [3]. Quinoline derivatives posses useful biological activities such as anti malarial, anti-inflammatory, antibacterial, anticancer, anti-microbial, anthelmintic, anti-fungal besides wide range of pharmacological activities [4-14]. Chloroquinoline compound has been used as prophylactics to prevent the development of malaria [15]. Chalcones and their derivatives are also medically important. Many chalcones compounds are important class of natural products and as a precursor for synthesis of various heterocyclic compounds like imidazole, pyrazoles, pyrazoline, azetidine, triazole, thiazole and oxadiazole [16-19] have been reported to posses anti-malaria, anti-inflammatory and anti-bacterial activity [20, 21] . Recently interest in the sulfur- heterocycles compounds have significantly increased since a wide range of biological activities [22] . This study aimed to synthesized new series of quinoline chalcones compounds and detect their antibacterial activity.

2. Materials and methods

2.1. Instrumentation

Melting point was recorded on electro thermal CIA9300 melting point apparatus. The *Proton nuclear magnetic resonance* (^{1}HNMR) to identify the structure and ^{13}CNMR spectra were recorded on nucleic magnetic resinous model ultra shield 400MHZ, Bruker Co, Germany using TMS as internal reference and DMSO-d6 as solvent . IR spectra were recorded on infrared spectrophotometer model Tensor 27.Bruker Co. Germany by using KBr disc .

2.2. Synthesis of 2-chloro-3-formyl quinoline(1) [23]

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To solution of acetanilide (5 mM) in dry DMF (15 mM) at 0-5C° with stirring $POCl_3$ (60 mM) was added drop wise and then hte mixture was stirred at 80-90 °C for 16h . The mixture was poured into crushed ice, stirred for 1h and the resulting solid filtered, washed well with water and re-crystallization from ethyl acetate to give pure compound .

Yield: 75% pale yellow M.P 148-151°C. FT.IR (KBr, ν cm^{-1}): 1668(C=O), 1562(C=N), 796(C-Cl) ,2780(C-$H_{aldehyde}$), figure (1) show chart of IR for compound(1) 3055(Ar-C-H).^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm) 7.61-7.65 (t,1H,C_7), 7.84-7.91(t,1H,C_6), 7.95-8.00 (d, 1H,C_8), 8.04-8.08 (d, 1H,C_5), 8.73(s, 1H,C_4), 10.5(s, 1H, HC=O), figure (II) show chart of ^{1}H NMR for compound(1) ^{13}CNMR: 126.46 (C_3), 126. 62 (C_6), 128. 23 (C_8), 128. 64 (C_5), 129. 81 (C_9), 133. 70 (C_7), 140. 39(C_4), 149.67 (C_{10}), 150.91(C_2), 189.20 (C=$O_{aldehyde}$), figure (III) show chart of ^{13}C NMR for compound(1).

2.3. Synthesis of 4-(benzyl thio) acetophenone (2) [24]

Potassium hydroxide (2.24g , 40 mM) was added to solution of benzylthiol (4.96g , 40 mM) in 15 ml of absolute ethanol. The mixture was heated to reflux until KOH had completely dissolved and then cooled to room temperature. A solution of 4-fluoro acetophenone (5.52g , 40 mM) in 20 ml of absolute ethanol was added drop wise and the mixture was heated to reflux for 12h. when cooled to room temperature the precipitate was filtered and washed with water and re-crystallization from ethyl acetate as white needles yield 85% M.P (111-113°C).U.V. $\lambda_{max}CHCl_3$ 242, 308. FT.IR (KBr, ν cm^{-1}): 1672(C=O), 1578(C=C).^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm) 3.26 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.30-7.88 (m, 9H, -Ar-H).

2.4. Synthesis of 4-(benzyl sulfonyl) acetophenone(3) [24]

4-(benzylthio) acetophenone(2) (2.19g , 8 mM) was dissolved in (50ml) of acetic acid. To this solution was added (8 ml) of 30% aqueous hydrogen peroxide drop wise with stirring then the mixture left over night at room temperature . A white precipitate had offered then the reaction mixture was poured into (40 ml) of ice water, the solid was formed filtered and washed with water yield 85% M.P (176-179°C). U.V. $\lambda_{max}CHCl_3$ (250, 284). FT.IR (KBr, ν cm^{-1}): 1678(C=O), 1314, 1149(SO_2).

2.5. Synthesis of 1-(4-(benzylthio) phenyl)-3-(chloroquinoline-3-yl) prop-2-en-1-one (4) and 1-(4-(benzyl sulfonyl) phenyl)-3-(chloroquinoline-3-yl) prop-2-en-1-one (5) [24]

2-chloro-3-formyl quinoline (7 mM) was added to an ethanolic solution (25ml) of compound (2) and compound (3) (7 mM) .

To the above reaction mixture, aqueous NaOH (0.39g in 3ml of water) was added drop wise with stirring the reaction mixture was kept over night at room temperature. The result solid was filtered off washed with water, then dried and recrystalizied from ethanol to afford compounds (4 and 5) .

Compound (4) yield 70% M.P (182-185°C).UV. $\lambda_{max}CHCl_3$ 242, 334. FT.IR (KBr, ν cm^{-1}): 1653(C=O), 1585(C=C), 1561(C=N), 747(C-Cl) .

^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm) 7.41 (d,1H,Hα), 7.82(d, Hβ), 7.43-7.46 (t, 1H,H-7), 7.56-7.59 (t, 1H,H-6) , 7.68-7.71(d, 1H, H-8) , 7.83-7.86(d, 1H, H-5) , 8.41(d, 1H, H-4), 7.91-8.66 (m, 9H, -Ar-H) figure (IV) show chart of ^{1}H NMR for compound(5).

Compound (5) yield 65% M.P (203-205°C). U.V. $\lambda_{max}CHCl_3$ 248, 318. FT.IR (KBr, ν cm^{-1}): 1655(C=O), 1597(C=C) , 1338,1146(SO_2), 3035(Ar-H), 1565 (C=N), 756(C-Cl) .^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 7.48 (d,1H,Hα) ,7.89 (d,1H,Hβ), 7.39-7.42(t, 1H, H-7), 7.51-7.54 (t, 1H,H_6), 7.64-7.69 (d, 1H, H-8),7.80-7.83 (d, 1H, H-5), 8.36(s, 1H, H4), 7.81-8.62(m, 9H, -Ar-H).

2.6. Synthesis of 1-(4-(benzylthio) phenyl)-2,3dibromo-3-(chloroquinoline-3-yl) propane-1-one (6) and 1-(4-(benzyl sulfonyl) phenyl)-2,3dibromo-3-(chloroquinoline-3-yl) propane-1-one (7) [25]

To solution of compound (4) and (5) (2 mM) in 15ml of dry CH_2Cl_2 cooled in ice bath to 0 C° , was added drop wise with micro-syringe over aperiod of 30minutes, (0.1 ml) of bromine and the mixture allowed to stand under stirring over night, the solvent was removed under reduced pressure and the residue was purified by re-crystallized by using ethanol .

Compound(6): yield 55% yellow solid M.P (172-175°C).FT.IR (KBr, ν cm^{-1}): 1685(C=O), 1572(C=N), 765(C-Cl), 2795(C-H), 3050(Ar-H).^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.91 (d,1H,C_2Br) ,4.95 (d,1H, C_3Br), 7.53-7.56(t, 1H, H-7), 7.75-7.79 (t, 1H,H_6), 7.85-7.88 (d, 1H, H-8),7.91-7.94 (d, 1H, H-5), 8. 61 (s, 1H, H4), 7.71-8.56 (m, 9H, -Ar-H).

^{13}CNMR: (DMSO-d_6) 127.1 (C_7), 127.8 (C_5), 128 (C_6), 129. 6 (C_8), 129. 3 (C_9), 147. 0 (C_4), 149. 3 (C_{10}), 150.0 (C_2), 193.53 (C=O), 122. 49 (C_3),141.3(C_2H), 152.1(C_3H), 148.2(CH benzene), 122.49(CH benzene), 135 (CH benzene), 128 (CH benzene), 137 (CH benzene), 121.1 (CH benzene), 121.6 (CH benzene), 106.2 (CH benzene), 125.1 (CH benzene), 112.3 (CH_2) .

Compound (7) 65% yellow solid M.P (186-188°C). FT.IR (KBr, ν cm^{-1}): 1689(C=O), 1585(C=N), 2870(C-H), 3055(Ar-H), 1320, 1155(SO_2).^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.22 (d,1H,C_2Br) ,4.66 (d,1H, C_3Br), 7. 31-7.35(t, 1H, H-7), 7.60-7.64

(t, 1H, H_6), 7.71-7.33 (d, 1H, H-8),7.72-7.75 (d, 1H, H-5), 8. 45(s, 1H, H4), 7.65-8.22 (m, 9H, -Ar-H).

2.7. Synthesis of 3-(3-(4-(benzylthio) phenyl)-1-H-pyrazol-5-yl)-2-chloroquinoline (8) and 3-(3-(4-(benzyl sulfonyl) phenyl)-1-H-pyrazol-5-yl)-2-chloroquinoline (9) [24]

A mixture of compounds (4,5) (2 mM) and hydrazine hydrate (6 mM) in ethanol (25 ml) was refluxed for 6h the reaction mixture was cooled and left over night at room temperature. The precipitate was filtered and re-crystallized from ethanol to give compounds (8 and 9) .

Compound 8 yield 55% M.P (189-191ºC).U.V. $\lambda_{max}CHCl_3$ 264, 292. FT.IR (KBr, ν cm^{-1}): 3222(NH) 1671(C=N), 3055(Ar-H). ^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.36 (s,1H, pyrazoline) , 7.64-7.66(t, 1H, C7), 7.71-7.73 (t, 1H,H_6), 7.83-7.86 (d, 1H, C-8),7.95-7.98 (d, 1H, C-5), 8.52(s, 1H, C4), 7.51-8.10(m, 9H, -Ar-H), 9.08(s,H,NH) .

Compound 9 yield 70% M.P (185-187ºC).U.V. $\lambda_{max}CHCl_3$ 244, 320. FT.IR (KBr, ν cm^{-1}): 3339(NH) , 1577(C=N), 1345,1149 (SO_2) .^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.38(s,1H,pyrazoline) , 7.66-7.69(t, 1H, C7), 7.74-7.77 (t, 1H,H_6), 7.85-7.91 (d, 1H, C-8),7.99-8.04 (d, 1H, C-5), 8.55(s, 1H, C4), 7.51-8.11(m, 9H, -Ar-H), 9.11(s,H,NH) .

2.8. Synthesis of 3-(3-(4-(benzylthio) phenyl)-1-acetyl-1H-pyrazol-5-yl)-2-chloroquinoline (10) and 3-(3-(4-(benzyl sulfonyl) phenyl)-1-acetyl-1H-pyrazol-5-yl)-2-chloroquinoline (11) [24]

A mixture of compounds (4) and (5) (2.0 mM) and hydrazine hydrate in(6.0m mole) in glacial acetic acid (10ml) was refluxed for 8h then the reaction mixture was cooled and poured into ice-water (25 ml) . The precipitated was collected and re crystallized from ethanol to give compounds (10 and 11).

Compound 10 yield 50% M.P (182-184ºC).U.V. $\lambda_{max}(CHCl_3)_2$ 244, 322. FT.IR (KBr, ν cm^{-1}): 1650(C=O) 1589(C=N), 3085(Ar-H). ^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 2.25(s,3H,CH_3), 5.42(s,1H in pyrazoline) , 7.72-7.76(t, 1H, C-7), 7.08-7.14(t, 1H,H-6), 7.86-7.89 (d, 1H, C-8),8.10-8.15 (d, 1H, C-5), 8.62 (s, 1H, C-4), 7.62-8.61 (m, 9H, -Ar-H) .

Compound 11 yield 65% M.P (235-238ºC). U.V. $\lambda_{max}CHCl_3$ 244, 318. FT.IR (KBr, ν cm^{-1}): 1662(C=O) 1586(C=N), 1315, 1147(SO_2) 3065(Ar-H). ^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 2.29(s,3H,CH_3), 5.31(s,1H in pyrazoline) , 7.68-7.71(t, 1H, C-7), 7.76-7.79 (t, 1H,H-6), 7.89-7. 91 (d, 1H, C-8),8.02-8.06 (d, 1H, C-5), 8.66 (s, 1H, C-4), 7.55-8.21 (m, 9H, -Ar-H) .

2.9. Synthesis of 3-(3-(4-(benzylthio) phenyl)-1-phenyl-1H-pyrazol-5-yl)-2-chloroquinoline (12) and 3-(3-(4-(benzyl sulfonyl) phenyl)-1-phenyl-1H-pyrazol-5-yl)-2-chloroquinoline (13) [24]

A mixture of chalcones (4 and 5) (2.0 mM) and phenyl hydrazine (4.0 mmol)in ethanol (25 ml) was refluxed for 10 hrs .The reaction mixture was concentrated to half under vacuum . The precipitate which separated on cooling was re-crystallized from ethanol to give compounds (12 and 13).

Compound 12 yield 65% M.P (198-201ºC).U.V. $\lambda_{max}(CHCl_3)$ 252, 374 FT.IR (KBr, ν cm^{-1}): 1595 (C=N), 3055(Ar-H). ^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.31(s,1H in pyrazoline), 7.73-7.78(t, 1H, C-7), 7.11-7.16(t, 1H,H-6), 7.86-7.89 (d, 1H, C-8),8.12-8.15 (d, 1H, C-5), 8.61 (s, 1H, C-4), 7.53-8.71 (m, 14H, -Ar-H) figure (V) show chart of ^{1}H NMR for compound(12) .

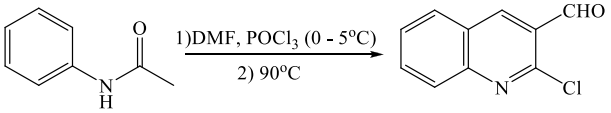
Compound 13 yield 70% M.P (215-218ºC).U.V. $\lambda_{max}CHCl_3$ 254, 398. FT.IR (KBr, ν cm^{-1}): 1591(C=N), 1312, 1124 (SO_2) 3055(Ar-H). ^{1}HNMR (400 MHZ, DMSO-d_6 , δ ppm), 5.31(s, H in pyrazoline ring) , 7.69-7.73(t, 1H, H-7), 7.77-7.8(t, 1H,H-6), 7.88-7. 91 (d, 1H, H-8),8.07-8.10 (d, 1H, C-5), 8.68 (s, 1H, C-4), 7.52-8.81 (m, 14H, -Ar-H) .

2.10. Antibacterial activity

The new compounds were evaluated for their antibacterial activities against two Gram-positive bacteria (*Staphelococcus aureus* and *Staphelococcus epidermidis*), two Gram-negative bacteria (*Escherichia coli* and *Proteus vulgaris*) at a concentration 10mg/disk. Ciprofloxacin at concentration of 10 mg /disk in dimethylsulfoxide were used as a positive control. After incubation period, the growth inhibition zones diameters were carefully measured in mm. The experiment has been done using a well plate of 6 mm. One Petri-dish subcultured for each pathogenic bacteria and used as a control (without testing for antibacterial activity), and incubation conditions were at 37 °C for 24 h. [30.31].

Results and discussion

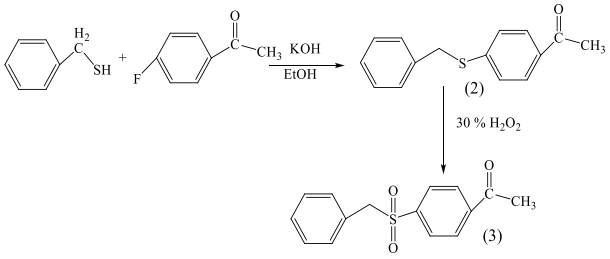
There are many routes have been developed for synthesized quinoline [26 , 27 , 28 , 29] the vilsmeier approach to be among the most efficient method to synthesized substituted quinoline, the starting material 2-chloro-3-formyl quinoline was synthesized from reaction of acetanilide with DMF / $POCl_3$. The valsmeier – Haack cyclization of acetanilide was carried out by adding $POCl_3$ to substrate in DMF at 0 – 5ºC followed by heating to 90ºC to afford compound(1) (scheme-1-)



Scheme – 1 –

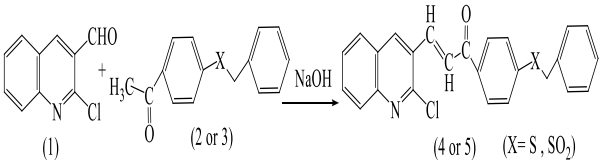
The IR spectra of compound (1) showed a sharp and strong absorption in 1668 cm^{-1} for carbonyl group and absorption at 1562 cm^{-1} for C=N group.

The H^1NMR of compound (1) showed a singlet at δ 10.5 for aldehydic proton, The C^{13}NMR spectra of this compound showed a carbonyl peak at δ 189.2 (benzothio) acetophenone (2) was synthesized from reaction of benzyl thiol and 4-fluoroacetophenone in the presence of KOH. Treatment of compound (2) with hydrogen peroxide(33%) in acidic medium gave 4-(benzyl sulfonyl) acetophenone(3) (scheme-2-).



SCHEME – 2 –

The IR spectra of compound(2) showed a strong band for carbonyl group at 1678 cm^{-1} . The H^1NMR of compound(2) showed two singlets at 3.26 and 4.32 δ for CH_3 and CH_2 respectively. Compound(3) showed strong band at 1672 cm^{-1} for carbonyl group and at 1314 cm^{-1} , 1149 cm^{-1} for SO_2 group 4-benzyl sulfonyl chalcone (4) and 4-benzyl sulfonyl chalcone (5) were synthesized by base catalyzed claisen – Schmidt condensation of 4-(benzyl thio) acetophenone (2) and 4-(benzyl sulfonyl) acetophenone (3) with 2-chloro-3-formyl quinoline (1) in ethanol and in the presence of aqueous sodium hydroxide (scheme-3)



Scheme – 3 –

The IR spectra of compound(4,5) showed a strong absorption bands at 1653 cm^{-1} and at 1655 cm^{-1} for carbonyl group and at reign (1585 , 1597cm^{-1}) for the presence of C=C and at (1561-1565 cm^{-1}) for C=N group and chalcone (5) showed absorption at (1338 , 1146 cm^{-1}) for SO_2 group. In the H^1NMR spectra of compounds (4,5) the protons of α,β-unsaturated carbonyl group appears as two doublets in the range of δ(7.41-7.48) for Hα and at range δ(7.82-7.89) for Hβ .

The smooth and selective bromination of chalcones (4,5) [26,27] afforded the corresponding dibromide (6,7) (scheme-4-)

The IR spectra of compounds (6,7) showed a strong absorption at (1685cm^{-1} and at 1689cm^{-1}) for carbonyl group and at 1320 cm^{-1} , 1155cm^{-1} for SO_2 group for compound (7) . The H^1NMR spectra data for compounds (6,7) showed absorption at δ 5.91 , δ 4.95 and at δ 5.22 , δ 4.66 as doublet for C_2HBr and C_3HBr respectively .

The reaction of chalcons (4,5) with hydrazine hydrate in absolute ethanol produce pyrazoline derivatives (8,9)(scheme-4-) . The IR spectra of compounds (8,9) showed absorption between (3222-3339 cm^{-1}) for NH and absorption at (1345,1149 cm^{-1}) for SO_2 for compound (9) and absorption between (1671-1577 cm^{-1}) for C=N . H^1NMR of compounds (8,9) showed a singlet absorption at δ 5.36 and at δ 5.38 for proton atom in pyrazoline , and a singlet at δ 9.08 and at δ 9.11 for NH proton whereas the reaction of chalcones (4,5) with hydrazine hydrate under reflux in glacial acetic acid afforded N-acetyl pyrazoline derivatives (10,11) (scheme-4-). The IR spectra of these compounds showed absorption between (1650-1662 cm^{-1}) for C=O group . H^1NMR spectra of these compounds showed a singlet signal between δ(2.25-2.29) for CH_3 group and absence of absorption at δ(9.01-9.08) for NH group .

The reaction of phenyl hydrazine with chalcones (4,5) afforded compounds (12,13) (scheme-4-) . The IR spectra of these compounds (12,13) showed absorption at (1595 cm^{-1} and 1591 cm^{-1}) for C=N group respectively . H^1NMR spectra of these compounds showed a single signal at δ 5.31 and δ 5.31 for hydrogen in the pyrazoline ring .

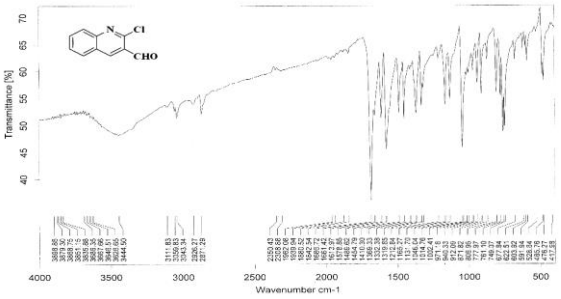


figure (1) show chart of IR for compound(1)

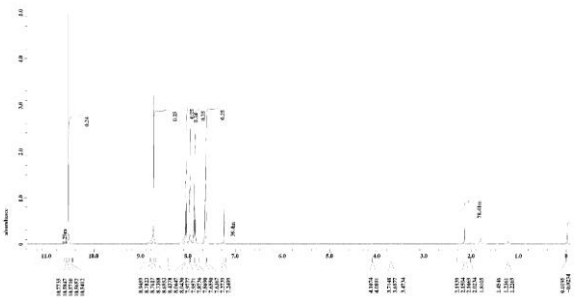


figure (II) show chart of ^{1}H NMR for compound(1)

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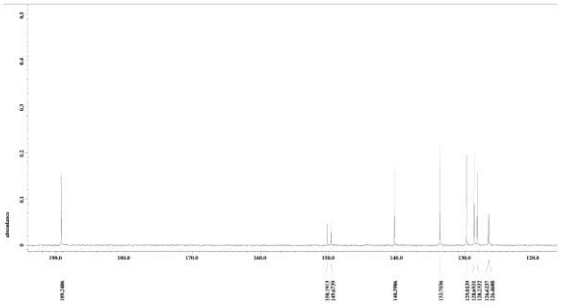


figure (III) show chart of ^{13}C NMR for compound(1)

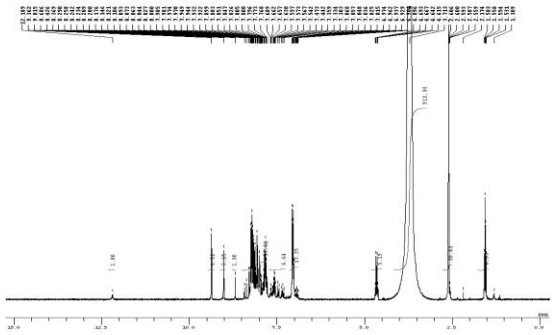


figure (IV) show chart of ^{1}H NMR for compound(5)

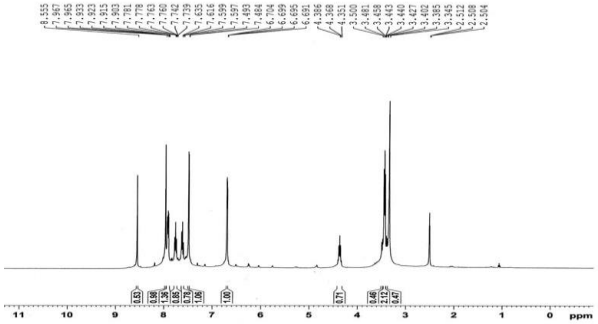
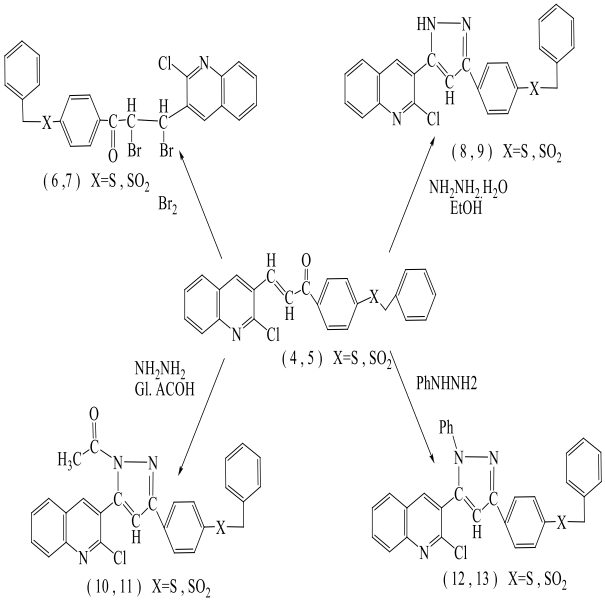


figure (V) show chart of ^{1}H NMR for compound(12)



Scheme – 4 –

Antibacterial activity

Based on their in vitro antibacterial activities, screening of the synthesized compounds is done by measuring the inhibition zone in terms of millimetre via the paper disc-agar diffusion technique. The newly synthesized compounds were screened for their antibacterial activities against two representative Gram – positive organisms (*staphylococcus aureus* and *staphylococcus epidermidis*), and two Gram – negative (*Escherichia coli* and *Proteus vulgaris*) by disc – diffusion method[12] ciprofloxacin was used as standard for comparison of antibacterial activities. Antibacterial tests were carried out by the agar diffusion technique [30, 31]. Antimicrobial activities were evaluated by measuring the diameter of zone of inhibition against test organisms at the end of 24 hours at 37ºC on the basis of observed zone of inhibition value , it can be concluded that there are a significant differences in the antibacterial potentials of prepared quinolinyl chalcones. The difference among the responses of different prepared compounds is also significant (table-1-). Among the prepared compounds (8-13) have shown more antibacterial activities against . The Gram – positive than rest of the compounds . this is might be because of structural features . the responses of the prepared compounds are less than standard .

Table – 1 – Antibacterial Activity data of compounds (4-13)

Comp.No.	Zone of inhibition in mm			
	S. aureus 10 mg / disk	*S. epidermidis* 10 mg / disk	*E. coli* 10 mg / disk	*Proteus Vulgar* 10 mg / disk
4	7	9	6	8
5	8	11	10	13
6	11	9	7	9
7	15	12	8	10

8	18	20	10	12
9	25	23	14	17
10	18	22	11	16
11	25	19	12	14
12	21	24	15	17
13	24	26	17	19
Control	26	28	24	25

Conclusion

We have developed a simple and efficient method for synthesis of some new quinolinyl chalcones containing sulfur atom and transferred pyrazolines derivatives . The newly synthesized compounds were evaluated for antibacterial activities , the results indicated that some of these compounds (8-13) have a good activity against the tested bacteria .

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