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Synthesis and biological activity of 2-chloro-3-formyl -1,8- naphthyridine chalcone derivative

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Abstract

Through a Vilsmeir-Haack cyclization reaction involving N-(pyridine-2-yl) acetamide, dimethylformamide, and phosphorous oxychloride, it has been possible to produce carbaldehyde of 2- chloro-1,8- naphthyridine (1). This procedure is both quick and effective. The chalcones (2a-e) produced by the Claisen-Schmidt compound (1) condensation with acetophenone, indole-2- acetyl, p-hydroxy acetophenone, furan-2-acetyl, and pyridine-3-acetyl are then with sulfoxide dimethyl treated existing there of one to two pieces of crystal iodine yielded iodochalconces (3a-e). The bromination of, chalcones gives compounds (4a- e). These compounds' structures were confirmed using IR and 1HNMR: Some compounds exhibited good activity against some types of bacteria.

Keywords: 1,8-naphthyridine , α,β-unsaturated carbonyl compounds , iodochalcone , dibromo compounds

1. Introduction

Due to the 1,8-naphthyridine skeleton's presence in numerous compounds derived from nature that have a variety of biological activities, 1,8-naphthyridine derivatives received a lot of interest [1] , Anew derivatives of 2-phenyl-7-methyl-1,8-naphthyridine by variable substitution at C_3 have been prepared and show activity against human breast cancer [2] , Naththyridine compounds are widely spread in natural products as tricyclic benzo(f)[3,4] Antitumor agents containing 1,8-naphthyridine have been considered promising [5,6,7] . Substituted 1,8-naphthyrdine are used as anti-inflammatory, antimalarial, antifungal and anti-bacterial[8,9,10] , 1,8-naphthyridine and quinolone represent acore for several vital drugs include in gemifloxacine[11], Naphthyridine compounds were show moderate cytotoxic effect against mice p338 lukemia When they were changed at the position of N-1 and N-7 [12,13]. The novel -2-chloro-3- formyl -1,5- naphthydine have been prepared and show a good activities as anti bacterial[13].

Now day the hetero Diels-Alder cyclization was the most efficient and powerful method used to prepare naphthyridine derivatives [14,15]. As is well known, some quinoline derivatives have been commonly used as raw materials for

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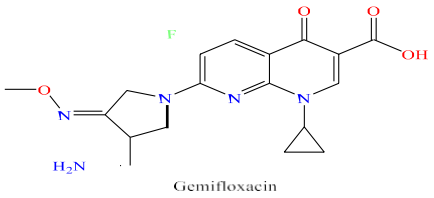
preparation of fused naphthyridine derivative[16,17] and 2,7 - functionalized ,1, 8-naphthyidine , noval triethylenglycol dinaphthyrodines have potential activity and they can be used as important binding units in the molecular design of some synthetic receptors.[18-19].Also some fluoro-1,8-naphthyridine derivatives are used in the treatment of memory disorders in Alzheimer's disease in particular. [20] .



Gemifloxacin

2. Experimental:

2.1. Instrumentation

The melting points were measured on elctrothermal CIA9300 Melting points device. 1H NMR was recorded on a 400 MHz NMR. The German Bruker company uses TNS as internal references and DMSO-d_6 as a solvent and using δ ppm for the values of chemical displacements. While the FT-IR spectroscopy registered on infrared spectrophotometer ModalTensor27 Germany of Bruker Co. .

2.2. Preparation of the-2-chloro-3-formyl - 1,8-,naphthyridine (1) [21]

Dissolved(5mmol) of N-(pyridine-2-yl) acetamide in (15mmol) of DMF. (60 mmol) of phosphorous chloride was added dropwise. The mixture was refluxed for 15 hours. With the stirring process continuing, pour in the ice water and filter out the resulting solid, Wash it with water, and recrystallize it from ethanol. in the form of a yellow substance powder (yield 56% ,m.p. 151-154 ºC). FT.IR (KBr γ cm^{-1}). 1690 (C=O), 2760(C-H), 675(C- Cl).While ^{1}HNMR spectra The following values are shown 9.50 (1H,s,CHO), 8.41 (1H,d,C-7), 7 .77(1H,s,C-4), 7.26-7.30(1H,d-C_5), 7.05-7.08(1H,t,C-6).

2.3. General practices for synthesis ofthe quinolinyl- chalcones (2a-e)[22]

The naphthyridenic compound (1) (1.06gm , 5mmoles) added to the solution of an ethanolic (15ml) of acetophenone, 2-acetyl furan, p-hydroxy acetophenone, 2-acetyl pyridine, and 3-acetyl indole (1.06 gm , 5mmoles). (40%, 3mmoles) from aqueous sodium hydroxide drop-wise added to the reaction mixture with stirring. The reaction was kept overnight then acidified with cold diluted hydrochloric acid. The solid resulted is filtered. With water washed and dried. Recrystallized from aqueous ethanol.

Preparation of -3-(-2-chloro-1,8- naphthiridine-2-yl)-1-(4-phenyl)prop-2-en--1-one)(2a): Yields 67%, FT.IR (KBr cm^{-1}). m.p.187-188 ºC. 1688 cm^{-1} (- carbonyl group). 1580cm^{-1}(- C=C- group). 760 cm^{-1}(C-Cl).^{1}HNMR spectra the following values are shown 8.85-8.89(1H,d,C7),7.69 (1H,s,C-4),7.60-7.65(1H,m,H_β),7.21-7.23 (1H,d,C-5),7.06-7.29 (1H,t, C-6), 6.96-6.99 (1H,m,H_α),7.29 7.35(5H,m,Ar-H).

Preparation of 3 - (2-chloro- 1,8- naphthiridine-2-yl)-1-(4-hydroxyphenyel) prop-2-,en-1- one) (2b) : Yields 61%, FT.IR(KBr γ cm^{-1}). m.p. 191-193 ºC. 1601cm^{-1} (-C=C-group).1690 cm^{-1}(carbonyl group).655cm^{-1}(-C-Cl-). While the ^{1}HNMR spectra the following data are shown,11.11(1H,s,OH), 8.858.88(1H,d,C-7), 7.78 (1H,s,C-4),7.51-7.55(1H,d,H_β),7.43,7.45(1H,d,C-5),7.15-7.19(1H,t,C-6),7.25-7.29(d,1H,Hα),6.96 - 7.31(4H,m,ArH).

Preparation of 3 (2-chloro -1,8- naphthyridine-2-yl) -1-(pyridine- 3- ,yl) prop- 2-en-1- one) (2c): YieldS 67%, m.,p. 262-264 ºC. FT.IR (KBr γ cm^{-1}). 1605 cm^{-1}(-C=C- group). 1685 cm^{-1} (carbonyl group). 650 cm^{-1}(C-Cl bond). The ^{1}HNMR spectra the following data are shown, 8.82-8.89(1H ,d,H-6 pyridine),8.42-8.44(1H,d,C-7),8.25-8.28(1H,d,H-5 pyridine), 7.82(1H,s,H-4), 7.71-7.75(3H,m,H_β),7.26-7.29(1H,d,C-5),7.1-**7.**11(1H,t,C-6),7.15 7.18(d,1H,H_α), 6.85-6.80(1H,t,H pyridine).

Preparation of 3 - (2-chluro-1,8- naphthiridine-2-yl)-1- furan-2-yl-prop-2-en- 1 - one) (2d): Yields 60%, m.p., 178-181 ºC. FT.IR(KBr γ cm^{-1}). 1596 cm^{-1} (-C=C-group).1688 cm^{-1} (carbonyl group). 675cm^{-1} (C-Cl bond).While the ^{1}HNMR spectra the following data are shown: 8.25-8.41(1H,d,H-7), 7.99-8.12 (1H ,s,C-4), 7.50-7.58 (1H,d, H_β),7.26-7.28(1H,d,C-5),7.15-7.19(1H,t,C-6),7.00-7.02(1H,d,H_α), 6.21-6.28(1H,m,C-2furan),6.15-6.20(1H,m,C-3furan),4.55-4.85(1H,m,C-4 furan).

Preparation of 3-(2-chloro-1,8-naphthiridine ,-2-yl)-1-(1H-indol-3-yl)prop-2-en-1-one) (2e) : Yields 80%, FT.IR (KBr γ cm^{-1}). m.p. 202-204ºC. 1605 cm^{-1}(-C=C-group).1688 cm^{-1}(carbonyl group) 674cm^{-1}(C-Cl). While the ^{1}HNMR spectra the following data are shown:9.92, (1H,s,NH),8.87 - 8.88 (1H,d,C-7), 7.80 (1H,s,C-4),7.52-7.55(1H,d,H_β),7.21-7.25(1H,d,C-5),7.18-7.29(5H ,m, H indol) , 7.12-7.18 (1H,t,C-6),7.25-7.28 (1H,d,H_α).

2.4. Synthesis of iodo chalcones (General procedure) (3a-e)[23]

(3 mmol) of chalcone (2a-e) was taken and (15 mL) of DMSO was added. An iodine crystal is added to this mixture, two drops of sulfuric acid are added and the reaction becomes acidic. The solution is infused for three hours, then it is poured into ice water, stirred for an hour, and the product is filtered. Wash with a solution (5%) of sodium thiosulfate and then with 25 ml of water, recrystallized from ethanol to yield compounds (3a-e).

Preparation of 1- (2-phenyl)-3 -(2-chloro-1,8- naphthiridine-3-yl)-3-iodoprop-2 -en-1-one) (3a): Yields 56%, FT.IR (KBr γ cm^{-1}). m.p. 233- 236 ºC. 1688 cm^{-1}(carbonyl group). 1485 cm^{-1} (-C=C- group).655 cm^{-1} (-C-Cl). The ^{1}HNMR spectra showed following data: ,8.66(1H,s,CH=CH), 8.31,8.32 (1H,d,C-7),7.92(1H,s,C-4),7.50-7.55(1H,d,C-5),7.25-7.28(1H ,t,C-6),7.09-7.66(5H,m,Ar-H) .

Preparation of 1-(2-hydroxyphenyl) 3-(2-chloro-1,8-naphthyridine-3-yl)-3-iodoprop-2-en-,1-onee) (3b) : Yields 66%, FT.IR (KBr γ cm^{-1}). m.p. 222-223ºC. 1689cm^{-1} (C=Ogroup). 3385(OH).1495cm^{-1}(C=C-group).750 cm^{-1}(C-Cl).The^{1}HNMRspectra showed the following values,11.1(1H,s,OH),8.91(1H,s,C=CH),7.95-8.83(1H,d,C -7), 7.61-7.66(1H,s,C-4), 7.01-7.39(5H,m,Ar-H) .

Preparation of 1 -(pyridine-3- yl) 3-(2-chloru-1,8-naphthyridine-3-yl) -3 -iodoprop-2- ,en- 1-one) (3c): Yields 61%,. m.p.233-235 ºC. FT.IR 1675 cm^{-1}(carbonyl group). 1495 cm^{-1}(-C=C group).755cm^{-1}(C-Cl).^{1}HNMR spectra showed following data:8.99(1H,s, -C=CH),8.65-8.68(2H,m,C-7, C-6 pyridine), 7.99(1H,s,C-4),7.81-7.88(1H,m,C_4pyridine),7.31-7.36 (1H,d,C-5),7.11-7.15(1H,t,C-6),6.90-6.96(1H,t, C_3 pyridine) .

Preparation of 1-(f uran-3- ,yl)-3,-(2- chluro-1, 8-naphthiridine-3-yl)-3- iodoprop- 2,-en-1- one-) (3d) : Yields 66%, FT.IR (KBr γ cm^{-1})., m.p. 259-261 ºC. 1591 cm^{-1} (-C=C group). 1688 cm^{-1} (-carbonyl group).750cm^{-1} (C-Cl). While the ^{1}HNMR spectra the following data are shown:8.91(1H,s,C=CH),8.86-8.88(1H,d,C-7),7.82(1H,s,C-4),7.51-7..57(1H,d,C 5), 7.14-7.19 (1H,t,C-6),6.51-6.58(1H,m,H_2 furan),6. 13-6.16(1H,m ,C_3 furan),4.21-4.30(1H,m,H_3 furan)

Preparation of 1- (H indol -3 –yl) 3 -(2-chloro-1,8,-naphthiridine-3-yl)-3-iodoprop - 2-en-1- one-) (3 e) : ,Yields. 91%, m.p,. 277-280 ºC. FT.IR values: 1688 cm^{-1} (carbonyl group). 1490 cm^{-1} (-C=C group). 755cm^{-1} (C-Cl). While the ^{1}HNMR spectra the following data are shown:9.91(1H,s,NH), 8.95(1H,s,C=CH),8.72-7.76(1H,d,C-7),7.71(1H,s,C-4),7.607.65(1H,d,C-5),7.50-7.59(5H,m,indol), 7.11-7.17(1H,t,C-6) .

2.5. Synthesis of dibromide (4a-e)[24]

In an ice bath, (0.1 ml) of bromine is gradually added for 30 minutes to a solution (3 mM) of (2a-e) in 15 ml of dry dichloromethane, stirring overnight. The solvent was evaporated in half by the evaporator. The precipitate is obtained. The resulting materials are purified by recrystallization using chloroform

Preparation of 2,3-dibrumo-1-phenyl-3- (2-chloro-1,5-naphthyridine) propane-1- one- (4a) : ,Yields 72%, FT.IR (KBr γ cm^{-1}). m.p. 130-131 ºC. 1695 cm^{-1}(C=O). 3055 cm^{-1} (Ar- H). While the ^{1}HNMR spectra the following data are shown:, 8.86- 8.88(-1H, d, C-7), 7.91 (-1H,s,C-4)7.82-7.88(1H,d,C-5),7.54-7.59(1H,t,C-6),6.96-7.22 (5H,m,Ar H),5.80,5.83(1H,d,C_2H Br),5.12-5.25(5H,d,C_3HBr) .

Preparation of 2,3-dibromo-1-(p- hydroxy phenyl)-3-(-2-chloro-1,5-- naphthiridine) -propane-1-one-, (4b) : Yields ,82%, FT.IR (KBr γ cm^{-1}). m.p. 180-183 ºC. 1691 cm^{-1}(C=O). 3058 cm^{-1} (Ar-H). ^{1}HNMR spectra the following data are shown:, 11.11(1H,s,OH) 8.91-8.98(1H,d,C-7), 7.89(1H,s,C-4), 7.20-7.28(-1H,d,C-5), 7.14-7.16 (-1H,t,C-6), 6.90-7.20(4H,m,Ar-H), 5.61-5.65(1H,d,C_2HBr), 5.15- 5.18(4H, m, Ar-H).

Preparation of 2,3- ,dibromo-1-(pyridine-3-yl)-3-(-2-chloro-1,5 –naphthiridine) propane-1-one- (4c): Yields, 45%,FT.IR (KBr γ cm^{-1}). m.p. 199-201 ºC. 1683 cm^{-1}(carbonyl group). 655 cm^{-1} (-C-Cl).

^{1}HNMR spectra gave following data are shown:,8.93-8.97(-1H,d,C-7) ,8.61-8.65(2H,m,C_6 pyridine), 7.89(1H,s,C-4), 7.76-7.79(1H,m,C_4pyridine),7.29- 7.34(1H,d,C-5)7.10-7.15(1H,t,C_6),6.88- 7.05(1H,m,C_3pyridine5.88-5.96(1H,d,C_2HBr), 5.91-5.94(1H,d,C-4),5.14-5.20(1H,d,CHBr), 5.00-5.05(1H,d,C_3HBr).

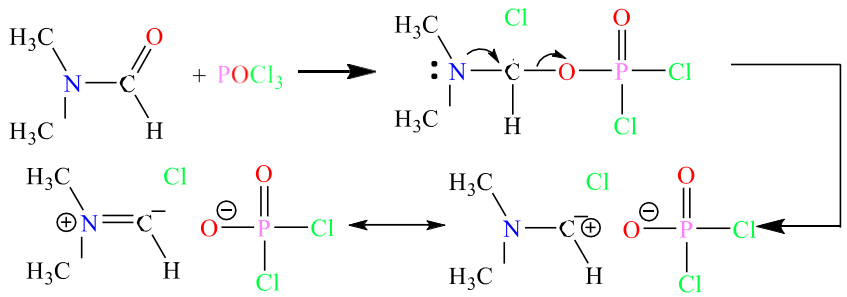
Preparation of 2,3-dibromo - 1- (- furan -3-yl),-3,-(-2-chloro-1,5-,naphthyridine) propane-1-one- (4d) : Yields ,69%, FT.IR m.p. 181-183 ^{o}C. (KBr γ cm^{-1}). 1666 cm^{-1}(-C=O). 755 cm^{-1}(-C-Cl). ^{1}HNMR spectra the following data are shown:, ,8.81-8.87(1H,d,C-7),7.80(-1H,s,C-4),7.60-7.66(1H,d,C-7), 7.51,7.58(1H,t,C-6),6.856.88(-1H,m, C_2furanal),6.64,6.66(1H,d,C_3furanal),5.85-5.91(1H,d,C_2HBr),5.16- 5.19(1H,d,C_3HBr), 4.65-4.66(1H,d,C_4 furanal).

Preparation of 2,3- dibromo- 1 - (1H-indol-yl)-3-(-2-chloro-1,5-,naphthiridine)propane-1-one- (4e) : Yields ,49.5%, FT.IR (KBr γ cm^{-1}). m.p. 251-254 ^{o}C. 1688 cm^{-1}(C=Ogroup). 655 cm^{-1}(C-Cl). ^{1}HNMR spectra the following data are shown:, 9.00(1H,s,NH),8.85-8.88(-1H,d,C-7), 7.89(-1H,s,C-4), 7.65-7.68(1H,d,C-5)7.51 7.53(5H,m,indol), 7.16-7.19(1H,t,C-6), 5.55-5.59(1H,d,C_2HBr), 5.20-5.28(1H,d,C_3HBr) .

3. Result and Discussion

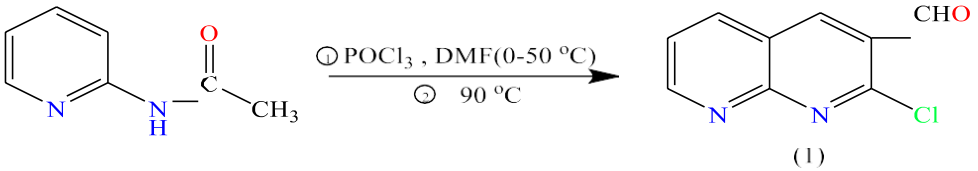
There are several methods for synthesizing 1,8-naphthyridine [25,26], but, it has been discovered that the Vilsmeier method is the most effective for attaining hetero annulation and beneficial transformation.

This method entails the production of electrophilic compensation on an activated ring of aromatic heterocyclic by the halomethylene iminium salt, conversion of these iminium species into some compounds of a new heterocyclic system. Starting compound compound 2-chloro-3-formyl-1,8- The naphthiridine was produced using reaction of N-(pyridine-2-yl)acetamide. by the Vilsmeier reagent which prepared from reaction dimethylformamide with $POCl_3$ according to mechanism show[27] in scheme (1)



Scheme 1: the formation of Vilsmeier-Haack reagent

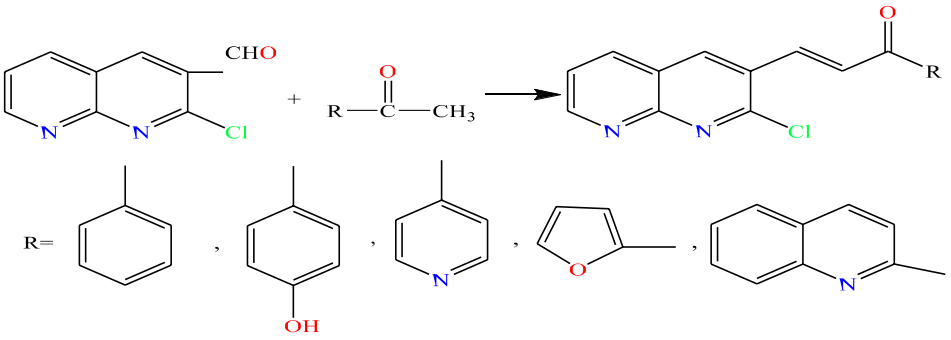
The cyclization of N-pyridyl acetamide was occur by adding drops from $POCl_3$ to dimethyl formamide at (0-5 ^{o}C) then heated to 90^{o}C scheme (2)



Scheme 2: preparation of compounds (1)

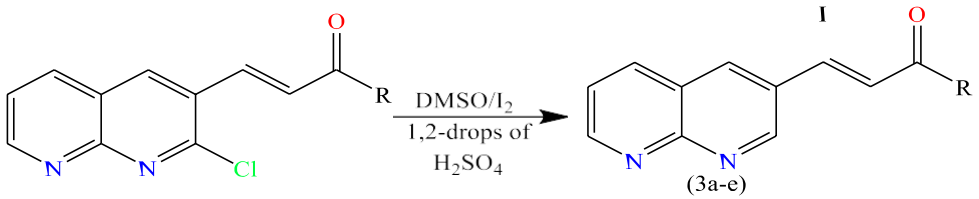
Physical , spectral data were used to determine the structure of starting compound (1). The IR spectra of these compound showed characterization bands at 1672cm^{-1} due to (C=O) group. ^{1}HNMR spectra for these compounds in dimethyl sulfoxide-d_6 show singlet at 10.54 ppm for the proton of aldehyde as shown in figure (1)

The compounds (2a-e) have beenprepared via clasien-schmidt condensation in ethanolic solution of 2-chloro-3-formyl-1,8-naphthyridine with acetophenone, p-hydroxy acetophenone, furan -2-acetyl, indole-2-acetyl and pyridine-3-acetyl to acquire the carbonyl compounds α,β-unsaturated [28] (chalcones) scheme(3)



Scheme 3: synthesis of chalcones compounds

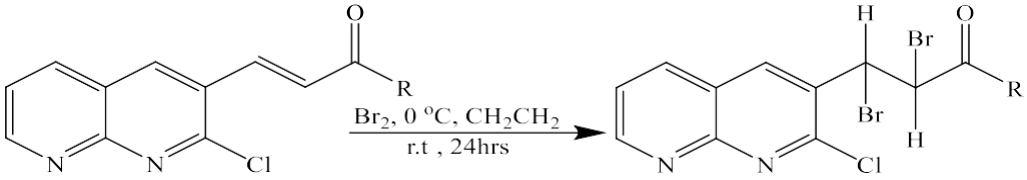
The IR spectra of these compounds (2a-e) showed a strong band at (1663-1680 cm^{-1}) for (C-Ogroup) and. at 3350 cm^{-1}due to OH group in compound (2b). The ^{1}HNMR spectra for these compounds (2a-e) showed a doublet peak at region (7.80-7.87ppm) and at region (7.90-7.97ppm) due to the proton of α and β respectively. And a singlet peak at (12.14ppm) for OH group for compound 2b as shown in figure 2,3 and 4 for compounds 2a,2b and 2e.Dimethyl sulfoxide in iodine is used as oxidizing agent and functions as an iodinating agent for α,β-unsaturated ketones. Iodine 1,2 crystals were added to a solution of chalcones (2a-e), which was then acidified with sulfuric acid.Then the solution was refluxed for one hour's [29] scheme (4)



Scheme 4: preparation of iodo compounds

IR spectra of these compounds (3a-e) showed a strong absorption at region (1665- 1675cm^{-1}) due to (carbonyl group) and ,3455 cm^{-1} for hydroxy group compound 3b.^{1}HNMR spectra showed a singlet signal at (11.11 ppm) for OH group for compound 3b and , singlet at region (8.81-8.91 ppm)due to the proton which attached to the ethanolic link age. The bromination of chalcones (2a-e) afforded dibromide (4a-e).

The reaction done by adding (0.1ml) of bromine to chalcones in dry methane dichloride with in an ice bath cooled under stirring (scheme 5).



Scheme (5)

FT-IR spectra for compounds (4a-e) revealed absorption at (1681-1695cm^{-1}) due to (-C=O) group and(3445 cm-1) for hydroxyl group for compound 4b. The ^{1}HNMR for these compounds (4a-e) showed two double at (5.11-5.19 ppm) and at (5.88-5.96 ppm) for the proton of CH_2Br and CH_3Br and showed singlet at (11.11 ppm) for OH group for compound 4b.

4. Biological studies

The new compound (3b, 3e, 4c, 4e) was screened for antibacterial activity (*Gram-negative* bacteria and *Gram-positive* bacteria). The antibacterial test was performed using the disc-diffusion method [30-31] Ciprofloxacin was used as a model for comparison. All compounds are found for display Good antibacterial activity. The result activities are listed in table (1)

Table (1) antibacterial activity data for some selected compounds(Control ciprofloxacin mg disc)

Compound No.	Staphylococcus aureus	Staphylococcus epldermids	E. coli	Proteus vagorie
3b	16	18	12	13
3c	18	18	13	15
4c	20	20	16	15
4e	16	12	14	12

4. Conclusion

In the present work compound(1) wasprepared by Vilismeier-Haack cyclization, the prepare compound condensed with different ketone to produce α,β-unsaturated carbonyl compounds. The reaction of chalcones with one crystal of iodine in the presence of DMSO produce iodo chalcones, dibromide compounds were prepared by bromination of chalcones. The compounds (2a,3b,e and ,4c,e) showed good antibacterial activity.)

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