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Synthesis, Antimicrobial and Molecular Docking Evaluation of Some Heterocycles Containing Quinoline Moiety

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ABSTRACT

A simple route for synthesizing tetrahydro-6-methylpyrimidine-one and – thione derivatives by condensation reaction of chloroquinolinecarbaldehyde. β-dicarbonyl compounds, as ethylacetoacetate or oracetylacetone and urea or thiourea in ethanol and acetic acid as a catalyst was used. On the other hand, pyroloquinolinone was obtained from the reaction of carbaldehydequinoline with formamide and fomic acid via Leuckart reaction. Moreover, chloroquinolinehydrazone was synthesized when carbaldehydequinoline reacted with hydrazine hydrate. Schiff base derivatives were prepared when chloroquinolinehydrazone was treated with substituted aldehydes. In addition 2-chloro-3-cyanoquinoline was prepared from dehydration of the aldoxime with thionyl chloride. Reaction of cyanoquinoline with hydrazine hydrate afforded 3-aminopyrazoloquinoline. This compound reacted with benzoylisocyanate and aldehyde derivatives to afford the corresponding N-(1H-pyrazolo[3,4-b]quinolone-3-ylcarbamoylbenzamide, N-((1H-indol-3-yl)methylene)-1H-pyrazolo[3,4-b]quinoline-3-amine,N-(naphthalen-2-ylmethylene)-1H-pyrazolo[3,4-b]quinolin-3-amine respectively. The antimicrobial evaluation and molecular docking of the synthesized compounds were screened, too

Keywords: chloroquinolinecarbaldehyde, β-dicarbonyl compounds, urea, thiourea, 3-aminopyrazoloquinoline, hydrazine hydrate, molecular docking, antimicrobial activity.

INTRODUCTION

Quinoline derivatives are very interesting in organic synthesis, due to their wide occurrence in natural products [1,2] and biological active compounds [3]. The heterocyclic compounds containing nitrogen atom particularly quinoline derivatives exhibited many pharmacological properties as anti-inflammatory[4], anti-bacterial [5], anti-fungal[6], antimalarial [7], anti-allergy [8], antidepressant[9], antiasthmatic [10], antitumor [11], neuroleptic activity [12], anti-hypertensive [13], cytotoxic [14], sedative [15], hypnotic [15], and bronchodilator activities [16]. Moreover, quinolines are presented in many commercial products, as pharmaceuticals and fragrances [17].Therefore, there is a great importance for the development of effective methods for synthesis of quinoline derivatives, due to the wide range of medicinal applications [17,18]. Moreover, 3,4-dihydropyrimidinone and thione exhibit widespread biological activities, as antihypertensive, antiviral, antitumor, antibacterial, antioxidant, α-1a- antagonism, anti-inflammatory agents [19, 20] and neuropeptide antagonists [21].Owing to these observations the present study was prompted to synthesize fused quinoline derivatives with anticipated antimicrobial activity using a facile methods.

MATERIALS AND METHODS

Melting points were determined with an electrothermal digital melting point apparatus (Electro- Thermal Engineering Ltd., Essex, United Kingdom). The IR spectra were recorded in KBr disks on a PyeUnicam SP 3300 and Shimadzu FT IR 8101 PC Infrared Spectrophotometers (PyeUnicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H NMR spectra were obtained from a Jeol ECA 500 MHz NMR Spectrometer (Tokyo, Japan) using deuterated dimethylsulphoxide (d_6-DMSO) as a solvent and (TMS) as an internal reference at 500 MHz. Mass spectra (EI-MS) were obtained with ISQ (Single Quadrupole MS, Thermo Scientific). Elemental analyses (C, H, N) results were recorded with Elementar Vario EL Germany and all of them agreed satisfactory with the calculated values. Solvents were dried/purified according to literature procedures.

General procedure for the synthesis of 3,4-dihydropyrimidinones 4a, 10a and thiones 4b, 10b:
A mixture of 2-chloro-3-formylquinoline **(1)** [22,23] (10mmol), ethylacetoacetate**(3)** or acetylacetone**(9)** (10mmol) and urea or thiourea**(2a, b)** (15 mmol) were dissolved in 50 (mL) of ethanol in the presence of acetic acid (1mL). The reaction mixture was refluxed for appropriate time (6-8h.). The progress of the reaction was monitored by TLC. Ethanol was distilled off and the resulting products washed well with water and dried then crystallized from ethyl acetate or ethyl alcohol to give products **4a, b** and **10a, b** respectively.

Ethyl-4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a):
Yield 67 %, yellow crystals, m.p. 217-218°C,IR (KBr, cm^{-1}): 3349 and 3223 (2 N-H), 1702 (C=O), 1648 (C=O, NH), 1625(C=N), 749 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 1.07 (t, 3H, $OCH_2\underline{CH_3}$), 2.33 (s, 3H, CH_3), 3.95 (q, 2H, $O\underline{CH_2}CH_3$), 5.42 (s, 1H, CH),7.56 (s, H, NH), 7.63- 8.10 (m, 5 H, Ar-H), 8.27 (s, 1H, NH). MS (*m/z, %)*: 345 (M^+, 11), 316 (M^+-(C=O), 18), 310 (M^+-Cl, 10), 280 (M^+-(Cl+2NH), 5), 272 (M^+-COOEt), 11). Anal. Calc.for $C_{17}H_{16}ClN_3O_3$ (345.78). Calcd: C, 59.05; H, 4.66; Cl, 10.25; N, 12.15.Found:C, 59.00; H, 4.52; Cl, 10.05; N, 12.01.

Ethyl-4-(2-chloroquinolin-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b):
Yield 63 %, deep red crystals, m.p. 233-234°C,IR (KBr, cm^{-1}): 3159 and 3124 (NH), 1679 (C=O), 1211 (C=S), 1615 (C=N), 745 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 1.14 (t, 3H, $OCH_2\underline{CH_3}$), 2.08 (s, 3H, CH_3), 3.20 (q, 2H, $O\underline{CH_2}CH_3$), 6.40 (d, 1H, CH), 7.12 (s, H, NH), 9.09 (s, 1H, NH). MS (*m/z, %)*: 361 (M^+, 3), 359 (M^+-2H, 11), 326 (M^+-Cl), 47), 317 (M^+-(C=S), 10), Anal.Calcd.for $C_{17}H_{16}ClN_3O_2S$ (361.78).Calcd: C, 56.43; H, 4.46; Cl, 9.80; N, 11.61; S, 8.86.Found:C, 56.22; H, 4.38; Cl, 9.65; N, 11.45; S, 8.74.

5-Acetyl-4-(2-chloroquinolin-3-yl)-3,4-dihydro-6-methylpyrimidin-2(*1H*)-one (10a):
Yield 65 %, brown crystals, m.p. 390-391°C, IR (KBr, cm^{-1}): 3263 and 2921 (2 NH), 1648 (C=O-CH_3), 1628 (C=O-NH), 1625 (C=N), 745 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.23 (s, 3H, CH_3), 2.50 (s, 3H,CO CH_3), 5.57. (s, 1H, CH), 7.20- 7.45 (m,5 H, Ar-H), 8.97 (s, 1H, NH),10.38 (s, 1H, NH). MS (*m/z, %)*: 279 (M^+-(HCl),6), 280 (M^+-(Cl), 4), 257 (M^+- (NH-CO-NH), 15). Anal.Calcd. for$C_{16}H_{14}ClN_3O_2$(315.75).Calcd: C, 60.86; H, 4.47; Cl, 11.23; N, 13.31. Found: C, 60.76; H, 4.35; Cl, 11.10; N, 13.11.

1-(4-(2-Chloroquinolin-3-yl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidin-5-yl)ethanone (10b):
Yield 61 %, yellow crystals, m.p. 156-157°C,IR (KBr, cm^{-1}): 3281 and 3140 (2 NH), 1577 (C=O), 1619 (C=N), 1137 (C=S), 753 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.32 (s, 3H, CH_3), 2.49 (s, 3H, CO CH_3), 6.23 (s, 1H, CH), 7.15- 8.19 (m, 5 H, Ar-H), 9.64 (s, 1H, NH), 10.56 (s, 1H, NH). MS (*m/z, %)*: 331 (M^+, 4), 296, 294 (M^+-Cl, 2), 287 (M^+-(C=S), 5), 257, 255 (M^+-thiourea, 13), 169 (M^+- (chloroquinolineC_9H_5ClN, 8). Anal.Calcd. for $C_{16}H_{14}ClN_3OS$ (331.82).Calcd: C, 57.91; H, 4.25; Cl, 10.68; N, 12.66; S, 9.66. Found:C, 57.80; H, 4.13; Cl, 10.54; N, 12.54; S, 9.53.

Reaction of thioxopyrimidine carboxylate 4b with hydrazine hydrate:
To a solution of 4-aryl-6-methyl-2-(thioxo)-1,2,3,4-tetrahydropyrimidine (2 mmols)**(4b)**, dissolved in 30 (mL) of ethanol, was added hydrazine hydrate (2 mL) the mixture was refluxed for 7h. The completion of reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue was treated with 50 mL water and filtered, the product washed well with water, dried and recrystallized from ethanol to produce product **5**.

4-(2-Chloroquinolin-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (5):
Yield 45 %, orange crystals, m.p. 145-146°C,^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.11 (s, 3H, CH_3), 5.46 (br, 2H,NH_2), 5.89. (s, 1H, CH), 7.63 (d,1H, NH),7.27-7.10 (m, 5H, Ar-H), 7.72 (br, 1H, NH), 9.46 (s, 1H, NH).MS (*m/z, %)*: 349(M^++2H, 17), 319(M^+ -CO, 8), 312(M^+ -Cl, 9). Anal.Calcd.for$C_{15}H_{14}ClN_5OS$(347.82). Calcd: C, 51.80; H, 4.06; Cl, 10.19; N, 20.13; S, 9.22. Found: C, 51.61; H, 4.01; Cl, 10.11; N, 20.04; S, 9.13.

Reaction of 2-aminophenol (6) with 4-ethyl 6-methyl-2-oxo-1,2,3,4-tetrahydro- pyrimidine-5-carboxylate (4a):
A mixture of **4a** (1 mmol) and 2-aminophenol**(6)** (1 mmol) in the presence of acetic acid (1 mL) was fused on a hot plate for 1h. The TLC confirmed that the reaction was completed.The reaction mixture was cooled. The crude product was crystallized from ethanol to give product **7**.

4-(2-chloroquinolin-3-yl)-N-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (7):
Yield 73%, deep brown crystals, m.p. 328-329 $^{\circ}$C, IR (KBr, *cm*$^{-1}$): 3346 (OH), 3340, 3217 (2NH), 3104 (NH), 1706 (C=N), 1644 (C=O), 1555(C=O-NH), 749 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.23 (s, 3H, CH_3), 5.37 (s, 1H, CH),6.14 (s,1H,NH),7.94 (s, 1H, NH),7.81-7.03 (m, 5H, Ar-H),6.73-6.64 (m, 4H, Ar-H),9.35 (s, 1H, NH-C=O), 9.85(s, 1H, OH, exchangeable withD_2O).MS (*m/z, %)*: 408 (M^+, 5), 393(M^+-NH, 3), 376 (M^{+1} –(NH+OH), 13) , 358(M^+- (Cl+NH), 5). Anal. Calcd. For$C_{21}H_{17}ClN_4O_3$ (408.84). Calcd:C, 61.69; H, 4.19; Cl, 8.67; N, 13.70. Found: C, 61.52; H, 4.15; Cl, 8.59; N, 13.55.

When the same reaction was carried out in ethanol and refluxed for 6 h. The TLC confirmed that the reaction was completed. Ethanol was distilled off and the resulting product washed well with water and dried then crystallized from ethyl acetate. Product **8** was isolated.

Ethyl-4-(2-chloroquinolin-3-yl)-N-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbimidate (8):
Yield 48 %, brown crystals, m.p. 135-136°C,^{1}HNMR (500 MHz, DMSO, δ , ppm):1.07 (t, 3H,$OCH_2\underline{CH_3}$), 2.33 (s, 3H, CH_3),3.98 (q, 2H, $O\underline{CH_2}CH_3$), 5.36 (d, 1H, CH),7.30-7.40 (m, 4H, Ar-H),7.33-7.47 (m, 5H, Ar-H), 7.55 (s 1H, NH), 7.67 (d,1H, NH), 7.70 (s 1H, OH). . MS (*m/z, %)*: 437 (M^{+1}, 25), 421 (M^+-(CH_3), 31), 408 (M^+-(CO),19), 393(M^+-(CH_3 +CO), 5).Anal.Calcd.for$C_{23}H_{21}ClN_4O_3$ (436.89).Calcd: C, 63.23; H, 4.84; Cl, 8.11; N, 12.82. Found: C, 63.11; H, 4.72; Cl, 8.01; N, 12.70.

Synthesis of *1H*-pyrolo[3,4-b]quinolin-3(*2H*)-one(11):
A mixture of 2-chloroquinoline-3-carbaldehyde **(1)**(10 mmol), formamide(4 mL) and formic acid (2 mL) were dissolved in (50 mL) ethanol. The reaction mixture was refluxed for 8h, and allowed to cool to room temperature. The TLC confirmed that the reaction was completed. The reaction mixture was diluted with ice and water, and then added a solution of sodium bicarbonate to neutralize the excess of acid, the product formed was filtered and crystallized from ethanol to produce the product **11**.

Yield 50 %, yellow crystals, m.p. 288-289°C,IR (KBr, cm^{-1}): 3417 (NH), 1655 (C=N), 1595 (C=O). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 4.16 (s, 2H, CH_2), 7.08- 8.18 (m,5 H, Ar-H), 8.46 (s, 1H, NH, exchangeable with D_2O).^{13}CNMR (125 MHz, d_6- DMSO, δ , ppm):166.78 (C=O), 161.96 (C=N), 135-115 (Ar-C), 39.48 (CH_2).MS(*m/z, %)*: 183 (M^+-H),13), 155 (M^+-(CO), 23), 173 (M^+-(CH_2+H) 72). Anal.Calcd. for $C_{11}H_8N_2O$(184.19).Calcd: C, 71.73; H, 4.38; N, 15.21. Found:C, 71.66; H, 4.32; N, 15.11.

Reaction of 2-chloroquinoline-3-hydrazone (12) with 2-naphthaldehyde (13) or *1H*-indole-3-carbaldehyde (15):
Amixture of hydrazone**12**(2 mmol) in ethanol(20 mL), was added to a solution of naphthaldehyde**(13)** or indole aldehyde **(15)** (2 mmol) in ethanol(20 mL). The reaction mixture was refluxed from 6-8 h. TLC monitored the progress of the reaction. The reaction left to cool overnight. The precipitate formed filtered, washed well with water and crystallized from ethylacetate, products **14** and **16** were isolated in good yields.

2-Chloro-3-(((naphthalen-2-ylmethylene)hydrazono)methyl)quinoline (14):
Yield 65%, yellow crystals, m.p. 305-306°C, IR (KBr, cm^{-1}): 1610 (C=N, quinoline), 1580 (2 C=N, hydrazone), 739 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 7.60-7.98 (m, 7H, Ar-H), 8.37 (s, 1H, CH=N) 8.13- 8.60 (m,5 H, Ar-H),8.91 (s, 1H, CH=N)MS (*m/z, %)*: 343 (M^+), 8), 308 ((M^+-Cl),100) 303 ((M^+-($C=N_2$),47), 281 ((M^+-($Cl+N_2$+ H), 78). Anal.Calcd.for$C_{21}H_{14}ClN_3$(343.81).Calcd: C, 73.36; H, 4.10; Cl, 10.31; N, 12.22. Found: C, 73.25; H, 4.01; Cl, 10.23; N, 12.11.

3-(((*1H*-Indol-3-yl)methylene)hydrazono)methyl)-2-chloroquinoline (16):
Yield 68%, yellow crystals, m.p. 292-293°C, IR (KBr, cm^{-1}): 3405 (NH), 1613 (C=N, quinoline), 1583(2 C=N, hydrazone), 738 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 7.20 -7.49 (m, 5H, Ar-H)7.27 (s, 1H, CH=N),8.00-8.06 (m, 5H, Ar-H), 9.06(s, 1H, CH=N, indole),11.88 (s,1H, NH). MS (*m/z, %)*: 332 (M^+, 6), 297 ((M^+-Cl), 6)Anal.Calcd.for$C_{19}H_{13}ClN_4$ (332.79).Calcd: C, 68.57; H, 3.94; Cl, 10.65; N, 16.84. Found: C, 68.45; H, 3.88; Cl, 10.54; N, 16.79.

Synthesis of(2-chloroquinolin-3-yl)methanamine (19):
A suspension of Lithium Aluminium hydride in 20 mL of dry *THF* was added drop- wise with stirred over a period of 20 min. To a solution of 2-chloro-3-cyanoquinoline **(18)** [24] in *THF* (2 mmols). The reaction mixture was refluxed for 4h (monitored by TLC). The reaction mixture was cooled then added few drops of ethyl acetate to get ridof the excess of the $LiAlH_4$. A saturated solution ofpotassium sodium tartarate was added. Then the product was filtered. The filtrate was evaporated and crystallized from ethanol to give compound **19**.

Yield 75 %, yellow crystals, m.p. 192-193°C,IR (KBr, cm^{-1}): 3407 (NH_2), 1613 (C=N), 752 (C-Cl). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 2.46 (s, 2 H,CH_2), 7.96-8.08 (m, 4H, Ar-H), 8.09 (s, 1H, Ar-H),9.91(t, 2H,NH_2), MS (*m/z, %)*:192 (M^+, 4), 190 (M^+-(2H), 23), 153 (M^+-(2H+Cl), 100), 155 (M^+-(2H+Cl), 15),127 (M^+-(CH_2+NH_2+Cl),13), 125 (M^+-(CH_2+NH_2+Cl),56).Anal.Calcd.for$C_{10}H_9ClN_2$ (192.64).Calcd: C, 62.35; H, 4.71; Cl, 18.40; N, 14.54. Found:C, 62.16; H, 4.55; Cl, 18.12; N, 14.32.

Synthesis of N-(*1H*-pyrazolo[3,4-b]quinolone-3-ylcarbamoylbenzamide (22):
To a solution of3-amino-*1H*-pyrazoloquinoline **(20)**[1] (1mmol) in methylene chloride was added (15 mmol) of benzoylisocyanate**(21)**and drops of triethylamine. Then the reaction mixture was stirred for 6h. Left to cool overnight, theprecipitate was filtered and crystallized from ethanol to give product **22**.

Yield 75%, brown crystals, m.p. 258-260°C,IR (KBr, cm^{-1}): 3366 (N-NH), 3180 (NH-C=O), 3051 (NH-COPh), 1660, 1615 (2 C=N), 1577, 1506 (2 C=O). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 7.45- 7.79 (m,5 H, Ar-H), 8.02-8.80 (m,4H, Ar-H), 8.76 (s, 1H, Ar-H), 8.91 (s, 1H, (NH-CO-NH), exchangeable with D_2O), 10.51 (s, 1H, NH-COPh, exchangeable with D_2O), 11.99 (s, 1H, NH-N, D_2O exchangeable).^{13}C NMR (125 MHz, d_6- DMSO, δ , ppm):168.64 (C=O-Ph),156.89 (C=O-NH), 154.73 (C=N-NH),149.16 (C=N-N), 129.42-125.29 (Ar-C). MS(*m/z, %)*:331 (M^+, 3), 184 (M^+-start), 48), 148 (M^+- start), 49). Anal.Calcd.for$C_{18}H_{13}N_5O_2$ (331.33).Calcd: C, 65.25; H, 3.95; N, 21.14; Found:C, 65.12; H, 3.88; N, 21.04.

Reaction of pyrazoloquinoline 20 with 2-naphthaldehyde 13 or indolaldehyde 15:
A solution of pyrazoloquinoline**(20)**[1] (1mmol) in ethanol (20 mL) was added to a solution of2-naphthaldehyde **13** or indole-3-aldehyde **(15)** (12 mmol) and 3 drops of glacial acetic acid. The reaction mixture was refluxed for 6 h, the reaction was monitored by TLC, then left to cool and poured into ice and water, the solid formed was filtered, washed well with water and crystallized from methanol to furnish compounds**23** and **24**.

N-((*1H*-Indol-3-yl)methylene)-*1H*-pyrazolo[3,4-b]quinolin-3-amine (23):
Yield 62%, pale brown crystals, m.p. 309-310°C, IR (KBr, cm^{-1}): 3187 (NH, indole), 3109 (NH, pyrazole), 1654 (C=N, quinoline), 1622 (C=N, indole), 1575 (C=N, pyrazole). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 7.14 (s,1H, CH=N), 7.18-7.34 (m, 5H, Ar-H), 7.89-8.30 (m, 5H, Ar-H), 8.30 (s, 1H, CH, indole ring), 8.87 (s, 1H, NH, indole, exchangeable with D_2O), 11.68 (s, 1H, NH, pyrazole, D_2O exchangeable). MS(*m/z, %)*: 310 (M^+- (1H), 3), 268 (M^+-(CH=N-indole ring), 6).Anal.Calcd.for$C_{19}H_{13}N_5$(311.34). Calcd: C, 73.30; H, 4.21; N, 22.49. Found: C, 73.76; H, 4.13; N, 22.36.

N-(Naphthalen-2-ylmethylene)-*1H*-pyrazolo[3,4-b]quinolin-3-amine (24):
Yield 65%, pale orange crystals, m.p. 219-220°C, IR (KBr, cm^{-1}): 3121 (NH, pyrazole), 1616 (C=N, quinoline), 1590 (C=N, pyrazole). ^{1}HNMR (500 MHz, DMSO, δ , ppm): 7.58 (s,1H, CH=N), 8.00-8.34 (m, 7H, Ar-H), 8.58-6.89 (m, 5 H, Ar-H), 13.25 (s, 1H, NH, D_2O exchangeable). MS(*m/z, %)*:322 (M^+, 5), 321 (M^+- (1H), 4),320 (M^+-(2H), 5), 308 (M^+-N, 68), 307 (M^+-NH, 28), 281 (M^+(2N +CH), 62). Anal.Calcd.for$C_{21}H_{14}N_4$(322.36).Calcd: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.03; H, 4.29; N, 17.22.

RESULTS AND DISCUSSION

Although several methods have been introduced for functionalized quinoline derivatives. The starting compound 2-chloroquinoline-3-carbaldehyde **(1)** was synthesized by *Vilsmeier Haack* reaction [22,23]. When compound **1** was reacted with urea or thiourea**2a,b** and active methylene compounds as ethylacetoacetate**(3)** or acetylacetone**(9)** in ethanol and in the presence of drops of acetic acid as a catalyst in one-pot reaction namely *Biginelli* reaction [19,20]. The corresponding compounds ethyl-4-(2-chloroquinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimi- dine-5-carboxylate**(4a)**, ethyl-4-(2-chloroquinolin-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4b)**, 5-acetyl-4- (2-chloroquinolin-3-yl)-3,4-dihydro-6-methylpyrimidin-2*(1H)*-one **(10a)**, and 1-(4-(2-chloroquinolin-3-yl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidin-5-yl)ethanone **(10b)**were obtained respectively. When aldehydequinoline**1** was treated with urea or thiourea, ethylacetoacetate and acetic acid, cyclocondensation reaction occurs with the formation of dihydropyrimidinone**4a** and dihydropyrimidinthione**4b**. This reaction can be considered as straightforward method for the synthesis of pyrimidinone and thione. The structure of compounds **4a**

can confirmed on the basis of elemental analysis and spectroscopic data. The IR spectrum of compound **4a** exhibited bands at 3349 and 3233 (2 NH), 1702 (C=O), 1648 (C=O- NH) and 1625cm^{-1} (C=N). Its MS spectrum showed an ion peak at *m/z* (%) 345(M$^+$, 11). Next the reaction of aldehyde **1** with acetylacetone, urea or thiourea under similar reaction conditions, products **10a**and **10b** were isolated (Scheme1).

In addition, the reaction of hydrazine hydrate with thioxotetrahydropyrimidine 5-carboxylate**4b**, 4-(2-chloroquinolin-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrim- idine-5-carbohydrazide **(5)** was obtained. Compound **5** is deduced from its elemental analysis, ^{1}H NMR and mass spectral data. The ^{1}HNMR spectrum revealed absorption bands at δ 2.11 (s, 3H, CH_3), 5.46 (br, 2H, NH_2), 7.72 (br, 1H, NH), its elemental analysis and molecular weight agree with formula $C_{15}H_{14}ClN_5OS$, *m/z* (%) = 349 (M$^+$ +2H, 17).

Moreover, condensation of compound **4a** with 2- aminophenol**(6)** in the presence of acetic acid by fusion afforded 4-(2-chloroquinolin-3-yl)-N-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(7)**.

Similarly, ethyl-4-(2-chloroquinolin-3-yl)-*N*-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2- 3,4-tetrahydropyrimidine-5-carbimidate **(8)** was produced when the same reaction was carried out under reflux in ethanol. Compounds **7**and **8** were supported by their elemental analyses,^{1}H NMR spectra and MS spectroscopy. The formation of compound **7**was confirmed spectroscopically by the absence of ethoxy proton in their ^{1}H NMR and IR spectra respectively and the appearance of NH-C=O at δ9.35 ppm and at 1555 cm^{-1} in its IR spectrum. While, the ^{1}H NMR spectrum of **8** showed bands at 1.07 (t, 3H, $OCH_2\underline{CH_3}$),3.98 (q, 2H, $O\underline{CH_2}CH_3$) which attributed to ethoxy proton. The mass spectrum of **7** showed an ion peak at m/z 408 (M$^+$, 5) and the MS of **8** (m/z, %) 437 (M^{+1}, 25) (Scheme 1).

(Scheme 1)

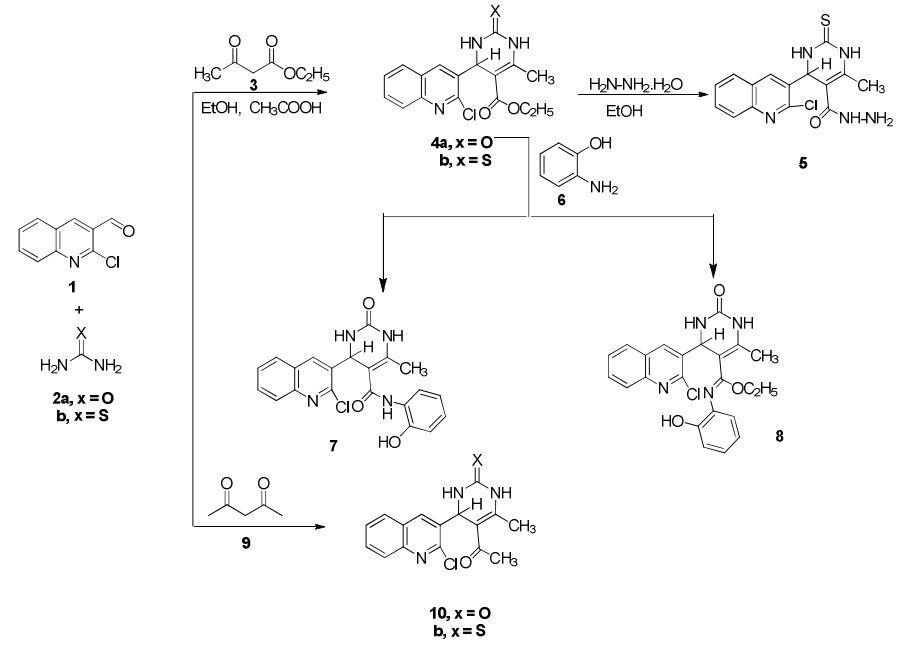
In fact formamide derivatives have many interesting properties in organic synthesis [23]. When carbaldehyde**1** was treated with formamide and formic acid at a preferred molar ratio that accelerate the reaction and to give a good yield. The reaction occurs *via Leuckart* reaction by using formamide as the usual formylating agent [25]. N-formyl derivative of the amine is formed, instead of the free amine when formamide is used in the *Leuckart* reaction[24,25]. Moreover, then nucleophilic formamide attacks the carbonyl carbon of the carbaldehyde. Protonation occurs for the oxygen from the nitrogen atom, then a water molecule is formed which it excluded forming N-formyl derivative as intermediate. Hydrogen chloride is expulsed from the reaction then cyclization occurs to form pyrrolo[3,4-b]quinolin-3(2H)-one (**11)**. Compound**11** was confirmed by IR, ^{1}H NMR and MS spectroscopy. The most important features in its spectroscopic data is the appearance of theNH and C=O bands at δ 8.46 ppm in the ^{1}H NMR spectrum and at 3417, 1595cm^{-1} in its IR spectrum (Scheme 2).

Various of *Schiff* base derivatives were prepared due to the antimicrobial properties. [26,27]. When aldehydequinoline **1**underwent condensation reaction with hydrazine hydrate afforded hydrazone**12** which on treatment with substituted aldehydes **13** and **15**, gave 2-chloro-3-(((naphthalen-2-yl)methylene) hydrazono)methyl)quinoline **(14)** and 3-(((*1H*-indol-3-yl)methylene)hydrazono)methyl)-2-chloroquinoline **(16)**respectively. The presence of an ion peak at m/z (%) 343(M$^+$, 8), in the mass spectrum of compound **14**, and an ion peak at m/z (%) 331(M$^+$-H) in the mass spectrum of compound **16** confirmed their structures(Scheme 2).

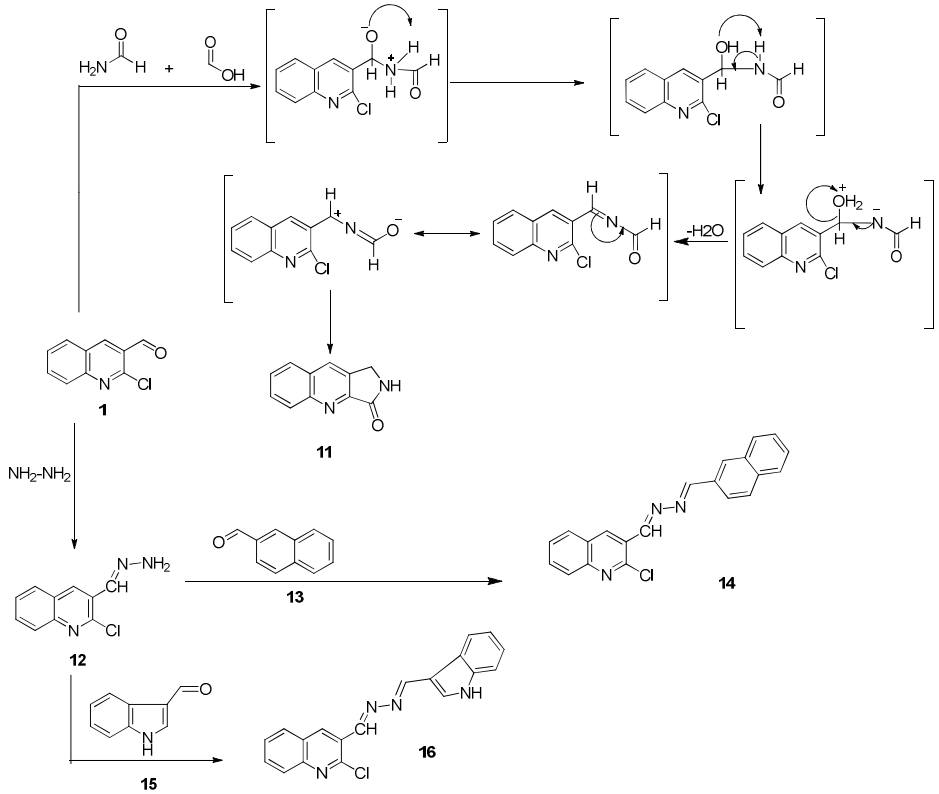
On the other hand, the formyl group in quinoline**1** can be converted into other interesting groups to produce new quinoline derivatives which are important in the synthesis of quinoline systems[28]. Therefore, the carbaldehyde group in **1**was transformed to a nitrile group via condensation reaction of **1**with hydroxylamine hydrochloride and sodium acetate to afford oxime**17**. Dehydration of the aldoxime**17** with thionyl chloride gave the cyanoquinoline**18** [28].Compound **18**was confirmed spectroscopically by the absence of the formyl proton in the ^{1}H NMR spectrum and appearance of nitrile group at 2228 cm^{-1}in the IR spectrum. In addition, lithium aluminium hydride is widely used in organic chemistry as reducing agent [29]. Therefore, the reaction of 2-chloro-3-cyanoquinoline **(18)** with lithium aluminium hydride and potassium sodium tartarate in *THF* afforded (2-chloroquinolin-3-yl)methanamine **(19)**. The reaction is occurred by reduction of cyanoquinoline group in **18** to primary amine with lithium aluminium hydride in *THF* [30,31]. The structure of **19**was determined according to its spectral data. A broad band at 3407*cm^{-1}* is assignabled to NH_2 in its IR spectrum. Signals at δ2.46 (2H, CH_2), and δ9.91 (2H, NH_2) in the ^{1}H NMR spectrum of **19**and its MS spectrum showed the molecular ion *m/z* (%) at 192 (M$^+$, 4).

In addition, cyclization of compound **18** with hydrazine hydrate, 3-amino-*1H*-pyrazoloquinoline **(20)**was obtained. N-(*1H*-pyrazolo[3,4-b]quinolone-3-ylcarbamoyl benzamide **(22)**was obtained from the reaction of compound **20** with benzoylisocyanate **21**. Evidence for formation of pyrazoloquinolone-3-ylcarbamoyl benzamide**22** is provided by the absorption bands of the 2 C=O in the IR spectrum at 1596 cm^{-1}, and its MS showed an ion peak at m/z 331(M$^+$, 3).

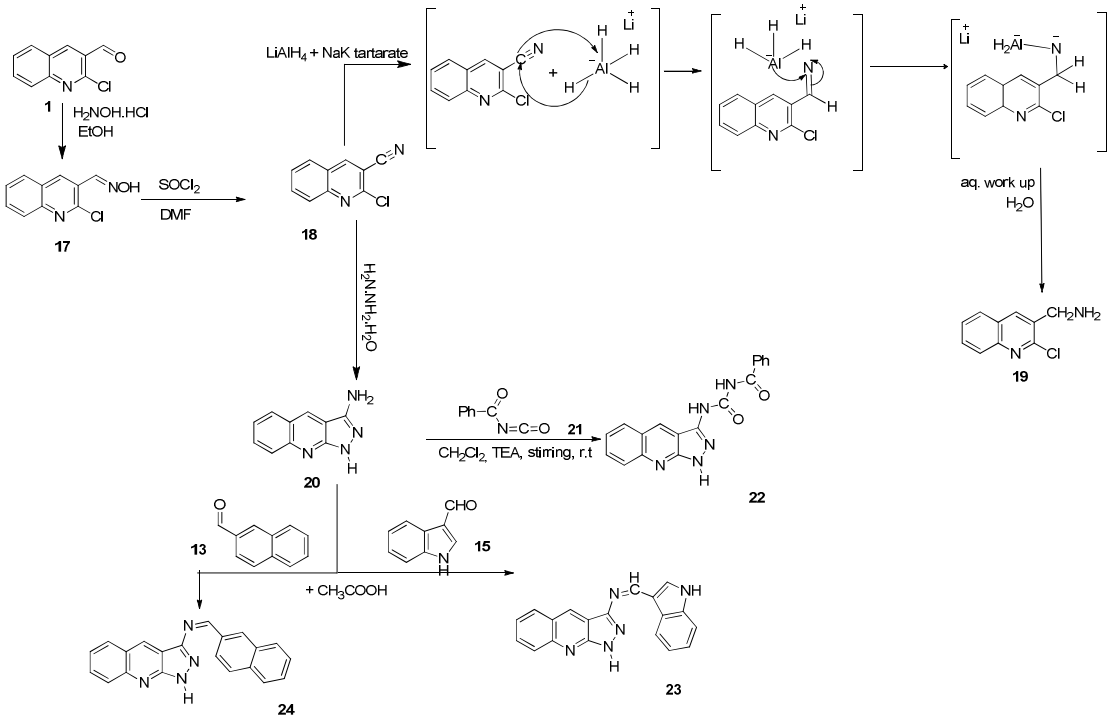
In the same manner pyrazoloquinoline *Schiff* base derivatives **23** and **24** were obtained in moderate yield by condensation reaction of **20** with naphthaldehyde **13** or indol-3-aldehyde **15**. The structure of compounds **23** and **24** produced from this reaction was based on their elemental analyses and MS spectra (Scheme 3).



Scheme (1)



Scheme (2)



Scheme (3)

ANTIMICROBIAL EVALUATION

The tested compounds **4a, 4b, 10a, 10b, 11, 14, 16, 20, 22, 23,** and **24** were evaluated as antimicrobial activity *in vitro* against gram-positive bacteria *Bacillus cereus*, *Staphylococcusaureus*, gram-negative bacteria *Pseudomonas aeuroginosa, Escherchia coli* and *Salmonella* by using *Penciillin* as reference standard. The solvent control used was DMSO. The antifungal activity was screened against *Candida albicans* by using *Nezo-arm* as reference standard. The inhibition zone for each compound were measured and evaluated by the reference. The obtained results of antimicrobial screening in table **(1)** indicate that compounds**11** and **13** are, the most active compounds against *B. cereus*, exceeding the inhibitory effect of the reference antibiotic, the clear inhibition zone reached 40 mm for compound **11** and 35 mm for compound **14** and it is considered a good result On the other hand, excellent antimicrobial activity was also achieved by compound **16** against the -ve gram strain pathogen, E. coli with clear zone higher than the reference antibiotic. Moreover, the other tested compounds showed different inhibitory effect with respect to the yeast pathogen *Candida albicans* in which the most antimicrobial effect was achieved by compound **11** reaching 50 % of the reference antibiotic, followed by compounds **20** and **22** showed clear zone of 18 mm.

Table (1): Inhibition zone(mm) for antibacterial and antifungal activities of some newly synthesized compounds

Microorganism inhibition zone diameter (mm)							
		Gram-positive bacteria		Gram-negative bacteria			Fungus
		Bacillus cerreus	*Staphylococcus aureus*	*Pseudomonas aeuroginosa*	*Escherichia coli*	*Salmonella*	*Candida albicans*
Comp	Ref.Antibio.*	30	30	20	15	15	40
4a		12	10	**15**	10	08	15
4b		15	00	00	12	12	14
10a		10	00	11	10	10	12
10b		00	15	**15**	12	10	15
11		**40**	09	12	00	10	20
14		**35**	10	14	10	12	00
16		00	15	10	**20**	**15**	12
20		00	15	10	09	00	18
22		00	00	11	12	12	18
23		00	12	15	13	08	14
24		00	12	00	12	08	12

** Reference antibiotics are Penicillin (antibacterial) and Nezo-arm (antifungal).*

On the other hand, compounds **4b**,**10b**, **22**, **23** and **24** showed moderate effect against *E. coli*. While, compounds **4a**,**10b** and **23** showed also moderate effect against *P. aeuroginosa*. Compounds **4b**, **14** and **22** revealed moderate effect against *Salmonella*, too.

MOLECULAR DOCKING

Docking studies were performed to assess the molecular affinity between the prepared compounds and the target proteins. The compounds **4b**, **10b**, **22**, **23** and **24** were studied to their affinity to the bacterial cell proteins as the DD-Trans peptidases.The crystallographic structure of the proteins (PDBs) were obtained front he protein data bank. All the docking was performed by the auto-dock tool.

The current docking results showed that the compounds **4b** and **10b** have the highest affinity to the proteins of the cell membrane of E. coli as they were 5 and 5.9 respectively. In addition, compound **4b** showed a high affinity of 5.9 in Salmonella. On the other hand, the compounds **4b** and compound **23** had the highest affinity in *Pseudomonas aeruginosa* as it was 7.3 for compound **4b** and 6.3 for compound **23**. *Staphylococcus aureus* was tested by compound **11**which showed a high affinity of 5.6. all the docking data suggest that compound **4b** has the strongest effect against the bacteria as it showed a high affinity to the proteins of the cell membrane.

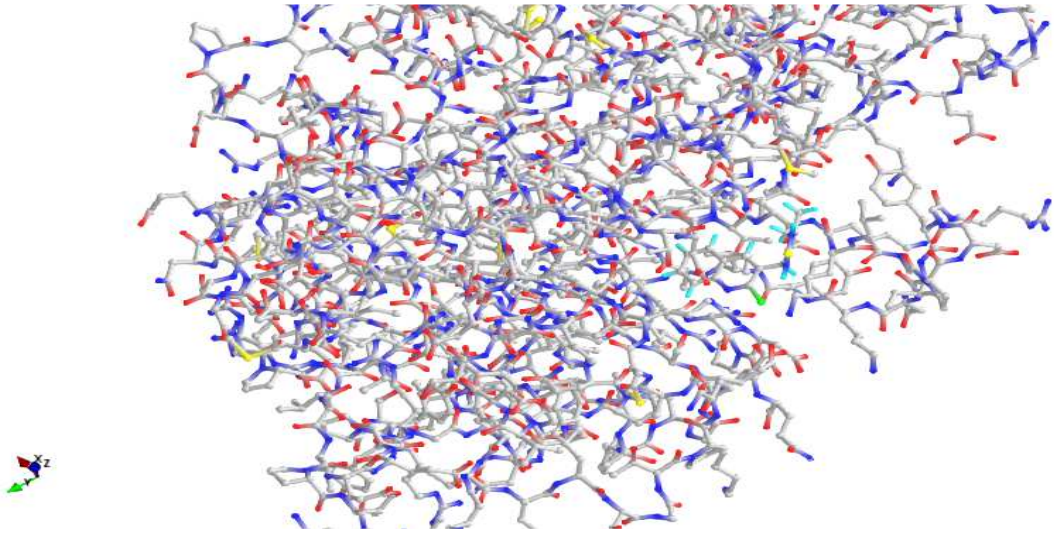


Fig. (1, 2): show the effects of compounds 4b and 10b on *E. coli, fig. 1*:refers to compound 4b

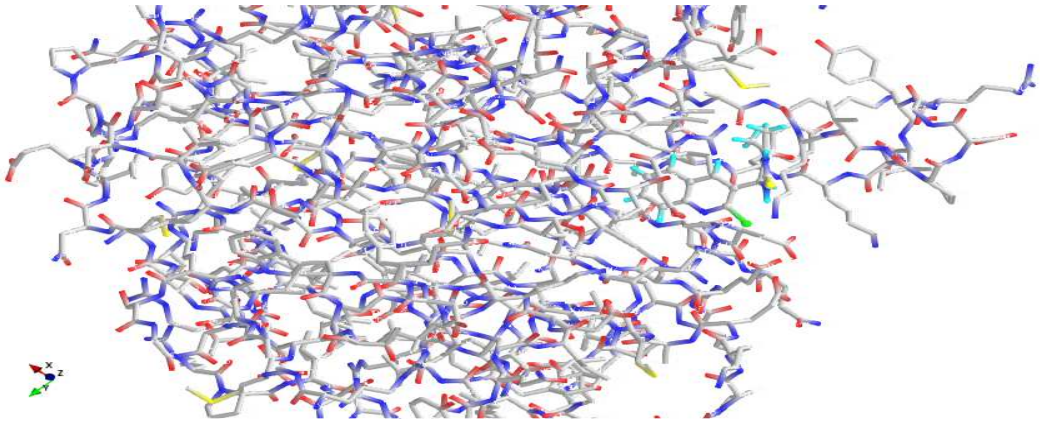


Fig. 2: refers to 10b, the compounds are shown in light blue color in both images

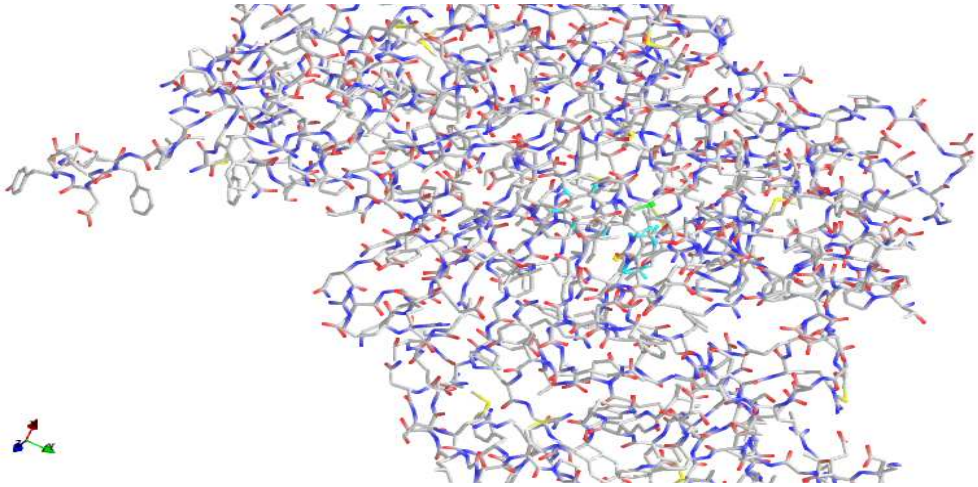


Fig. 3: shows the effects of compound 4b on Salmonella, the compound is shown in light blue color

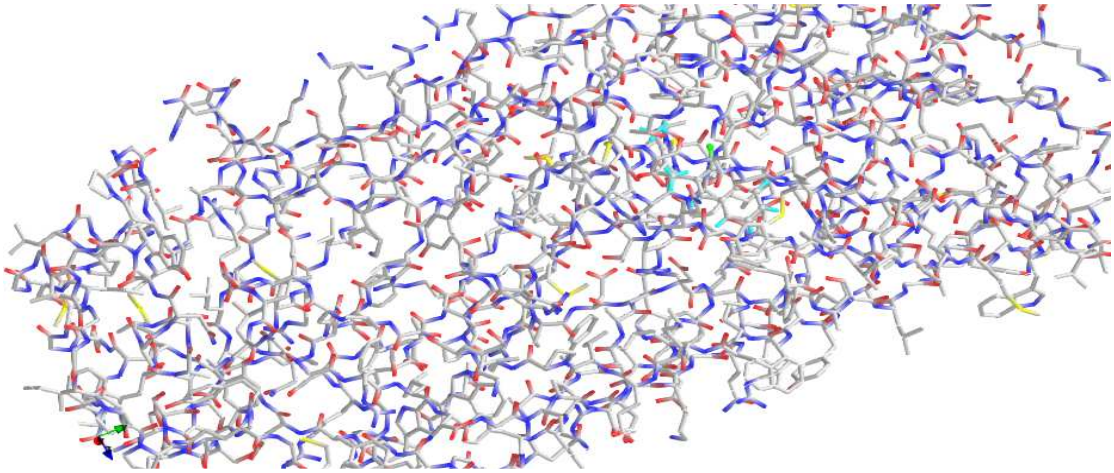


Fig. 4, 5: show the effects of compounds 4b and 20 on *Pseudomonas aeruginosa* and *fig. 4*refers to compound 4b

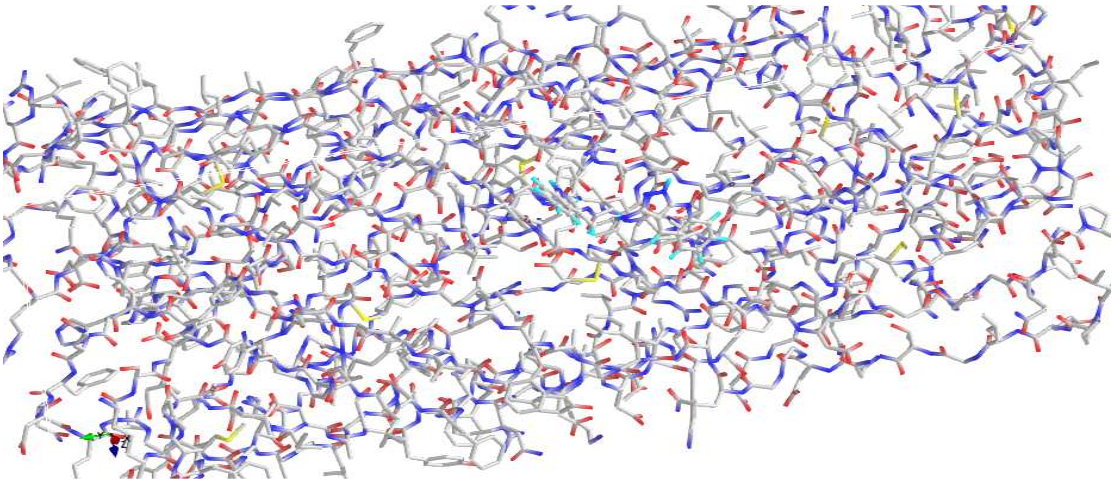


Fig 5: refers to 20, the compounds are shown in light blue color in both images

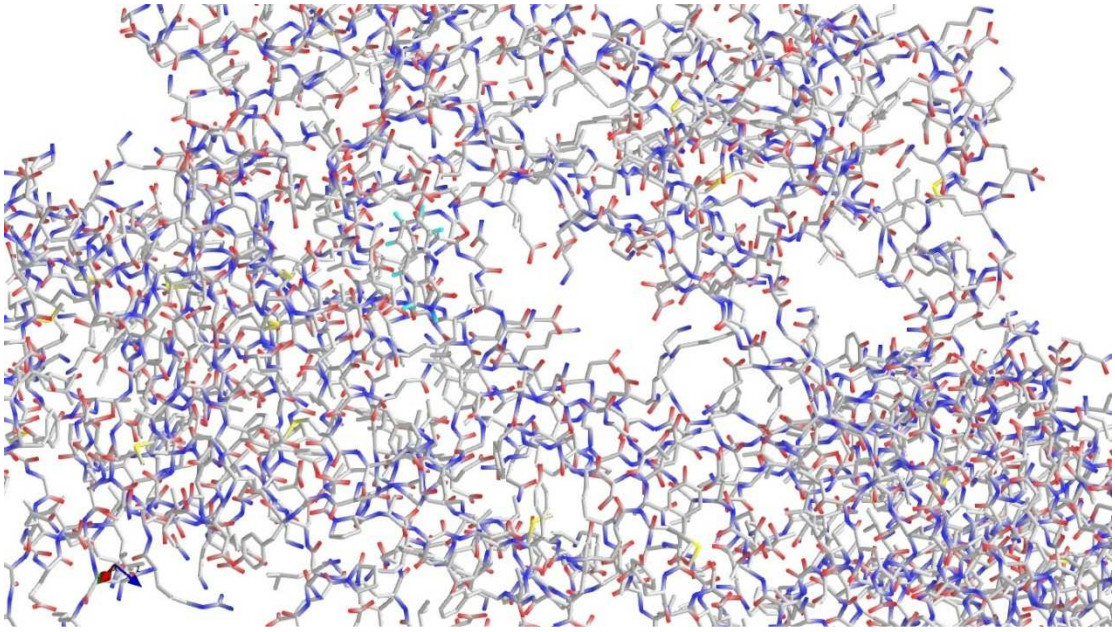


Fig. 6: shows the effects of compound 11 on Staphylococcus, the compound is shown in light blue color

Procedure

A disc of sterilized filter paper saturated with measured quantity (25 µL) of the tested sample (1 mg/mL final concentration) was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37^{o}C for 24 h for bacteria (in case of fungi, at 25^{o}C for 72 h), the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in chloroform as a solvent.

CONCLUSION

Some derivatives of quinoline have been studied for their antimicrobial activity. An efficient method for the synthesis of 3,4-dihydropyrimidinone and thione derivatives by using acetic acid as a simple and an easy catalyst when cyclocondensation reaction of the mixture of three components were refluxed in ethanol. Although several catalysts have been developed in this reaction [19,20, 32-35]. Moreover, various substituted *Schiff base* have been studied. The in vitro antimicrobial evaluation of the synthesized compounds were screened against some pathogenic strains of Gram positive bacteria, Gram negative bacteria and fungus. Compounds **11** and **14**, showed higher activity than the reference antibiotic against B. cereus. Excellent antimicrobial activity against E coli by compound **16** were observed. Moreover, other compounds showed also moderate effect against the pathogens.

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