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Synthesis, Molecular Docking and Antimicrobial Activities of 3-Formyl-2- (1H)quinolinone Schiff Base Derivatives and 3-(((3-Acetylphenyl)imino)- methyl)quinolin-2-(1H)-one Chalcone Derivatives

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Abstract

Some of Schiff base derivatives were separated by condensing 3-formyl-2-quinolinone with various primary amine derivatives in ethanol, in which water is expelled. Moreover, substituted acryloylphenyliminomethylquinolinone chalcone derivatives were prepared by the process of condensation reaction of aldehyde derivatives with 3-acetylphenylquinolinone in dilute solution of ethanolic sodium hydroxide via Claisen-Schmidt condensation method. Cyclization reaction of the quinolinone chalcones with malononitrile, phenylhydrazine, urea and thiourea were also investigated. The structures of these compounds have been elucidated on the bases of spectral data. The novel products were also evaluated for their antimicrobial activity.

Keywords: 2-Oxo-3-formaldehyde quinoline, primary amines, aldehydes, Claisen-Schmidt condensation, molecular docking, antimicrobial evaluation

Introduction

The significance of quinoline derivatives in biological and pharmacological activities has attracted much attention [1-4]. Thus, great efforts have been dedicated to synthesize functional derivatives of quinoline. It is conspicuous that 2-oxoquinoline is a type of alkaloid which exists in nature on a large scale like quinoline. Moreover, compounds with a 2-oxoquinoline nucleus structure have been discussed and they have been shown to possess preferable biological properties including anticancer, anti-inflammation, and anti-proliferation [5-7]. Schiff base derivatives are also multifunctional groups and they are able to enhance different biological and pharmacological properties like antibacterial [8-11], antifungal [11,12] and antitumor activities [13]. Moreover, Schiff bases are compounds having imine or azomethine (-HC=N-) functional group, and they constitute the backbone for several organic compounds and possess tremendous applications in many fields [14,15]. Furthermore, several studies demonstrated that the presence of lone pair of electrons on the nitrogen atom of the azomethine moiety in many compounds is of significant chemical and biological interests [16-19]. On the other hand, chalcone derivatives represent a class of chemical compounds which exist widely in a diversity of medicinal plants [20-21] and several of them have broad spectrum of pharmacological and biological characteristics as antimicrobial [21], anticancer [22], antitumor [23],

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antitubercular [24] and anti-oxidant agent [25]. As well, the presence of reactive α, β-unsaturated carbonyl system of chalcone derivatives is responsible for their chemical and biological activities [21-26]. Because of these findings, this paper prompted us to synthesize some novel Schiff base- and chalcone-derivatives containing quinoline moieties using simple methods. Moreover, the 2-oxoquinoline compound is selected as bioactive moiety and some of new derivatives are prepared. Antimicrobial activities are also evaluated *in vitro*.

Experimental

Chemistry

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 Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC Infrared Spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). ^{1}H and ^{13}C NMR spectra were obtained from a Jeol ECA 500 MHz (Tokyo, Japan), Brucker Avance 300 MHz and a Varian Mercury VXR-300 MHz NMR spectrometers using deuterated dimethylsulfoxide (d_6-DMSO) as a solvent and TMS as an internal reference at 300, 400, and 500 MHz (^{1}H NMR) and at 75.46, 100, and 125 MHz (^{13}C MNR) respectively using deuterated dimethyl sulphoxide (d_6-DMSO) as a solvent and (TMS) as an internal reference. Chemical shifts were related to that of the solvent. Mass spectra (EI-MS) were obtained with ISQ (Single Quadrupole MS, Thermo Scientific) and Shimadzu GCMS-QP EX mass spectrometer at 70 eV. 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.

Reaction of 3-formyl-2-(1H)quinolone (2) with different primary amines 3, 6, 8, 10, 12, 14, 16.
 General procedure
A solution of 3- formylquinolone **2** [27] (0.01 mol) in ethanol (25 mL) was added to a solution of 2-aminobenzenethiol **(3)**, thiazol-2-amine **(6),** 2-chloro-3-(hydrazonomethyl)quinoline **(8)**, (3-aminoacetophenone) **(10)**, 4-aminophenol **(12)**, 4-

aminobenzoic acid **(14)**, or N-aminorhodanine **(16)** (0.01 mol), respectively. The reaction mixture was refluxed for 4-8 h. The reaction was monitored by TLC. Left to cool and the precipitated formed was collected by filtration, crystallized from the suitable solvent, and compounds **5, 7, 9, 11, 13, 15,** or **17** were isolated, respectively. In case of *N*-aminorhodanine **(16)** the reaction occurred by adding drops of acetic acid and compound **17** was also obtained.

3-(Benzo[d]thiazol-2-yl)quinolin-2(1H)-one (5)
Crystallized from ethanol, yellow crystals, yield 82%, mp: 356-358 °C. IR (KBr, cm^{-1}): ν= 3439 (OH), 1660 (HO-C=N), 1556 (S-C=N). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 12.50 (s, 1 H, OH, D_2O exchangeable), 9.18 (s, 1H, H-4 quinolinone), 8.13-7.42 (m, 8 H, H-5, H-6, H-7, H-8, 4H, benzothiazole). MS (EI, 70 eV): *m/z* (%) 278 (M$^+$, 100), 279 (M$^+$ + H, 21), 280 (M$^+$ + 2H, 8). Anal. Calcd. For $C_{16}H_{10}N_2OS$ (278.33): C, 69.04; H, 3.62; N, 10.06; S, 11.52. Found: C, 69.00; H, 3.30; N, 10.00; S, 11.41.

3-((Thiazol-2-yliminomethyl)quinolin-2(1H)-one (7)
Crystallized from ethanol, yield 75 %, yellow crystals, mp: 250-252ºC. ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 11.88 (s, 1 H, NH, D_2O exchange able), 8.48 (s, 1 H, H-4, quinolinone), 8.27 (s, 1H, N=CH), 7.88- 7.43 (m, 4 H, quinolinone), 7.33 (d, 1H, J=8.0 Hz, =HC-N), 7.25 (d, 1 H, J=7.2 Hz, =CH-S). MS (EI, 70 eV): *m/z* (%) 257 (M$^+$+2H, 8.61), 256 (M$^+$+H), 1.73), 255 (M$^+$, 2), 227 (M$^+$-(C=O), 1.35). Anal. Calcd. For $C_{13}H_9N_3OS$ (255.30): C, 61.16; H, 3.55; N, 16.46; S, 12.56. Found: C, 61.00; H, 3.41; N, 16.32; S, 12.44 %.

3-(((2-Chloroquinolin-3-yl)methylene)hydrazono) methyl) quinolin-2(1H)-one (9)
Crystallized from acetone and petroleum ether (60-80 °C), yellow crystals, yield 77%, mp 331-332 °C. IR (KBr, cm^{-1}): ν= 3443 (NH), 1654 (HN-$\underline{C=O}$), 1608 (Cl-$\underline{C=N}$), 1563, 1483 (2 C=N-N), 752 (Cl-C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 12.12 (s, 1 H, NH, D_2O exchangeable), 9.14 (s, 1 H, H-4, chloroquinoline), 9.03 (s, 1 H, H-4, quinolinone), 8.25 (d, 1 H, J= 6.6 Hz, H-8, quinolinone), 8.01 (d, 1H, J= 8.4 Hz, H-8, chloroquinoline), 7.90 (s, 1 H, N=CH, quinolinone and chloroquinoline), 7.75-7.70 (m, H-6, H-7, chloroquinolinone), 7.38 (d, 1 H, J=

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8.4 Hz, H-5 chloroquinoline), 7.26-7.21 (m, 3 H, H-5, H-6, H-7, quinolinone). MS (EI, 70 eV): m/z (%) = 359 (M$^+$ - H, 85), 360 (M$^+$, 60). Anal. Calcd. For $C_{20}H_{13}ClN_4O$ (360.80): C, 66.58; H, 3.63; Cl, 9.83; N, 15.53 . Found: C, 66.33; H, 3.35; Cl, 9.71; N, 15.35%.

3-(((3-Acetylphenyl)imino)methyl)quinolin-2(1H)-one (11)

Crystallized from ethanol, yellow crystals, yield 85%, mp: 337-339 °C. IR (KBr,

cm^{-1}): ν= 3441 (NH), 1672 (CO-CH$_3$), 1555 (HN-<u>C=O</u>), 1489 (H-<u>C=N</u>). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.18 (s, 1 H, NH, D$_2$O exchangeable), 10.23 (s, 1 H, H-4, quinolinone), 8.47 (s, 1 H, N=CH), 7.90 (d, 1H, J= 8.1 Hz, H-8, quinolinone), 7.88-7.61 (m, 3H, H-5, H-6, H-7, quinolinone), 7.36-7.21 (m, 4H, Ar-H), 2.49 (s, 3H, COCH$_3$). ^{13}C NMR (75 MHz, d$_6$- DMSO, δ, ppm): 189.62 (<u>C</u>OCH$_3$), 161.30 (<u>C</u>O-NH), 142.31 (C=N), 142.00, 141.11, 133.52, 133.30, 130.76, 129.00,125.59, 122.52, 121.22, 118.04, 115.33 (Ar-C), 38.64 (C=O-<u>CH$_3$</u>). MS (EI, 70 eV): m/z (%) 290 (M$^+$, 100), 291 (M$^+$ + H, 17), 292 (M$^+$ + 2 H, 4), 246 (M^{+1} - (C=O-CH$_3$), 6), 171 (C$_{10}$H$_7$N$_2$O, 31). Anal. Calcd. For $C_{18}H_{14}N_2O_2$ (290.32): C, 74.47; H, 4.86; N, 9.65 . Found: C,74.22; H, 4.67; N, 9.51%.

3-(((4-Hydroxyphenyl)imino)methyl)quinolin-2(1H)-one (13)

Crystallized from ethanol, yellow crystals, yield 81%, mp: 267-268 °C. IR (KBr, cm^{-1}): ν= 3439 (br, NH+OH), 1654 (C=O), 1562 (C=N). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.08 (s, 1 H, NH, D$_2$O exchangeable), 9.56 (s, 1 H, OH, D$_2$O exchangeable), 8.78 (s, 1 H, H-4, quinolinone), 8.59 (s, 1 H, N=CH), 7.86 (d, 1H, J= 7.8 Hz, H-8, quinolinone), 7.83 (d, 1H, J= 7.8 Hz, H-5, quinolinone), 7.55-7.51 (m, 2 H, H-6, H-7), 7.36 (d, 2H, J= 7.8 Hz, Ar-H), 6.83 (d, 2H, J= 6.9 Hz, Ar-H). ^{13}C NMR (75 MHz, d$_6$- DMSO, δ, ppm): 161.53 (C=O), 156.56 (C- OH), 151.43 (C=N), 142.71 (C-N), 139.45 (C-NH), 136.41, 131.42, 129.30, 126.80, 122.5, 122.50, 119.46, 118.93, 115.79, 115.06 (Ar-C). MS (EI, 70 eV): m/z (%) = 264 (M$^+$, 100), 265 (M$^+$ + H, 19), 266 (M$^+$ + 2H, 4). Anal. Calcd. For $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.50; H, 4.51; N, 10.32 %.

4-(((2-Oxo-1,2-dihydroquinolin-3-yl)methylene) amino)benzoic acid (15)

Crystallized from ethanol, deep yellow crystals, yield: 82%, mp: 349 -350 C. ^{1}H- NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.19 (s, 1 H, OH, D$_2$O exchangeable), 12.15 (s, 1 H, NH, D$_2$O exchangeable), 10.24 (s, 1 H, H-4, quinolinone), 8.48 (s, 1 H, N=CH), 8.00 (d, 1 H, J= 8.4 Hz, H-8, quinolinone), 7.91 (d, 2 H, J= 7.8 Hz, Ar-H), 7.76-7.62 (m, 1H, H-7), 7.59 (d, 1H, J= 8.1 Hz, H-5, quinolinone), 7.36-7.24 (m, 1H, H-6, quinolinone), 6.55 (d, 2 H, J=8.4 Hz, Ar-H). MS(EI, 70 eV): m/z (%) = 292 (M$^+$, 100), 293 (M$^+$+H, 22), 294 (M$^+$+ 2H, 3). Anal. Calcd. For $C_{17}H_{12}N_2O_3$ (292.29). C, 69.86; H, 4.14; N, 9.58. Found: C, 69.72; H, 4.03; N, 9.43%.

3-(((2-Oxo-1,2-dihyroquinolin-3-yl)methylene) amino)-2-thioxothiazolidin-4-one (17)

Crystallized from acetone/ petroleum ether (60-80°C), orange crystals, yield: 75%, mp: 324 -326 °C, IR (KBr, cm^{-1}): ν= 3435 (NH), 1656 (HN-<u>C=O</u>), 1564 (=N-N-<u>C=O</u>), 1486 (C=N), 1243 (C=S), 1112 (C-S). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.23 (s, 1 H, NH, D$_2$O exchangeable), 9.07 (s, 1 H, H-4, quinolinone), 8.80 (s, 1 H, N=CH), 7.81(d, 1H, J= 7.8 Hz, H-8, quinolinone), 7.76 -7.57 (m, 1H, H-7), 7.35 (d, 1H, J= 7.8 Hz, H-5, quinolinone), 7.27-7.22 (m, 1H, H-6, quinolinone), 4.21 (s, 2 H, CH$_2$). MS (EI, 70 eV): m/z (%) =303 (M$^+$, 30), 304 (M$^+$ + H, 5). Anal. Calcd. For $C_{13}H_9N_3O_2S_2$ (303.36). C, 51.47; H, 2.99; N, 13.85; S, 21.14. Found: C, 51.33; H, 2.85; N, 13.43; S, 21.00%.

Condensation of 3-(((3-acetylphenyl)imino)methyl) quinolin-2(1H)-one (11) with different aldehydes 18, 20, 22, and 1

General procedure

A mixture of 3-(((3-acetylphenyl)imino) methyl)quinolin-2(1H)-one **(11)** (0.01mol) and the appropriate aldehyde, indol-3-aldehyde **(18)**, 4-hydroxy-3-methoxybenzaldehyde **(20)** 2-hydroxybenzaldehyde **(22)**, and or 2-chloro-3-formylquinoline **(1)** (0.01mol) was dissolved in ethanol (20 mL), and an aqueous solution of NaOH (40 %, 10 mL) was added dropwise with stirring at room temperature. The reaction mixture was refluxed gently for 4-6 h. The completion of reaction was monitored by TLC and it was kept overnight at room temperature. Then, it was poured onto crushed ice and acidified with aqueous HCl (10 %). The

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separated solid product was filtered off, washed well with water, dried, and crystallized from the proper solvent, to give chalcones **19, 21, 23** and **24**, respectively.

3-((E)-((4-((E)-3-(1H-Indol-3-yl)acryloyl)phenyl) imino)methyl)quinolin-2(1H)-one (19). Crystallized from ethyl acetate and petroleum ether (60-80 ºC), brown crystals, and yield 65 %, mp 289-290 º C. IR (KBr, *cm^{-1}*): ν= 3418 (br, 2 NH), 1643 (br, 2 C=O), 1509 (C=N). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.13 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 11.80 (s, 1 H, NH indole, D$_2$O exchangeable), 9.94 (s, 1 H, H-4, quinolinone), 8.11 (d, 1H, J= 9.0 Hz, H-8, quinolinone), 7.89 (d, 1H, J= 9.0 Hz, H-5, quinolinone), 7.67 (s, 1 H, N=CH), 7.53-7.48 (m, 4H, Ar-H), 7.37 (d, 1H, C̲H̲=CH-CO, J$^3_{HH}$ =15.1 Hz, β-ethylenic proton), 7.23 (d, 1H, CH=C̲H̲-CO, J$^3_{HH}$= 15.1 Hz, α-ethylenic proton), 7.24-7.21(m, 2H, H-6, H-7 quinolinone), 7.19-6.93 (m, 5H, indole). MS (EI, 70 eV): *m/z* (%) = 417 (M$^+$, 2). Anal. Calcd. For C$_{27}$ H$_{19}$ N$_3$ O$_2$ (417.46): C, 77.68; H, 4.59; N, 10.07. Found: C, 77.55; H, 4.43; N, 10.00 %.

3-((E)-((4-((E)-3-(4-Hydroxy-3-methoxyphenyl) acryloyl)phenyl)imino)methyl)quinolin-2(1H)-one (21). Crystallized from ethanol, brown crystals, yield 72 %, mp 380-381ºC. IR (KBr, *cm^{-1}*): ν= 3431 (br, OH, NH), 1516 (2 C=O), 1461 (C=N). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 9.77 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 8.60 (s, 1 H, H-4, quinolinone), 8.35 (s, 1 H, N=CH), 8.85 (d, 1H, C̲H̲=CH-CO, β-ethylenic proton), 7.70-7.44 (m, 4 H, H-5, H-6, H-7, H-8, quinolinone), 7.39-7.36 (m, 4 H, Ar-H), 7.41 (d, 1H, CH=C̲H̲-CO, α-ethylenic proton), 7.24-6.97 (m, 3 H, Ar H), 3.84 (s, 3 H, OCH$_3$), 3.45 (s, 1 H, OH, D$_2$O exchangeable). MS (EI, 70 eV): *m/z* (%) =424 (M$^+$, 10), 425 (M$^+$+ 1H, 23), 426 (M$^+$+2H, 12). Anal. Calcd. For C$_{26}$H$_{20}$N$_2$O$_4$ (424.45): C, 73.57; H, 4.75; N, 6.60. Found: C73.45; H, 4.54, N, 6.50%.

3-((E)-((4-((E)-3-(2-Hydroxyphenyl)acryloyl) phenyl)imino)methyl)quinolin-2(1H)-one (23). Crystallized from acetone and petroleum ether (60-80 ºC), brown crystals, yield 62 %, mp 355-356 ºC. IR (KBr, *cm^{-1}*): ν= 3431 (br, - OH, NH), 1643 (br, 2 C=O), 1446 (C=N). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.00 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 11.02 (s, 1 H, OH, D$_2$O

exchangeable), 10.26 (s, 1 H, N=CH), 7.67 (s, 1 H, H-4, quinolinone), 7.64 (d, 1H, J= 6.9 Hz, H-5, quinolinone), 7.51-7.43 (m, 4 H, Ar-H) 7.34 (d, 1H, J= 6.9 Hz, H-8, quinolinone), 7.41-7.32 (m, 1H, H-6, H-7, quinolinone), 7.29 (d, 1H, C̲H̲=CH-CO, J$^3_{HH}$ =15.3 Hz, β-ethylenic proton), 7.15 (d, 1H, CH=C̲H̲-CO, J$^3_{HH}$= 15.1 Hz, α -ethylenic proton), 7.10-6.93 (m, 4H, Ar H). MS (EI, 70 eV): *m/z* (%) =394 (M$^+$, 2), 356 (M$^+$ -(C-CH=CH), 6.8). Anal. Calcd. For C$_{25}$ H$_{18}$ N$_2$ O$_3$ (394.42): C, 76.13; H, 4.60; N, 7.10. Found: C, 76.00; H, 4.43; N, 7.00.

3-((E)-((4-((E)-3-(2-Chloroquinolin-3-yl)acryloyl)phenyl)imino)methyl)quinolin-2(1H)-one (24). Crystallized from acetone and petroleum ether (60-80 ºC), brown crystals, yield 72 %, mp 273-274 ºC. IR (KBr, *cm^{-1}*): ν= 3428 (NH), 1649 (C=O), 1612 (C=O), 1567, 1503 (2 C=N), 708 (C- Cl). ^{1}H NMR (300 MHz, DMSO-d$_6$, δ, ppm): 12.21 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 9.76 (s, 1 H, CH=N), 8.16 (s, 1 H, H-4, quinolinone), 8.14 (s, 1 H, H-4, chloroquinoline), 8.07- 7.98 (m, 4H, quinolinone), 7.92- 7.80 (m, 4H, chloroquinoline), 7.74 (d, 1H, C̲H̲=CH-CO, J$^3_{HH}$ =15.4 Hz, β-ethylenic proton), 7.72-7.67 (m, 4H, Ar-H), 7.64 (d, 1H, CH=C̲H̲-CO, J$^3_{HH}$ = 15.6 Hz, α-ethylenic proton). ^{13}C NMR (MHz, d6- DMSO, δ, ppm): 194.80 (C=O), 155.01 (C=O), 142.60 (2 C=N), 136.90, 134.73, 133.17, 132.92, 132.84, 131.01, 130.35, 129.69, 129.64, 129.48, 128.97, 128.67, 128.51, 128.48, 127.16, 126.99, 124.10, 116.67, 114.84, 113.10. MS (EI, 70 eV): *m/z* (%) =463 (M$^+$, 3), 427 (M$^+$ - (HCl), 3). Anal. Calcd. For C$_{28}$H$_{18}$ClN$_3$O$_2$ (463.91): 72.49; H, 3.91; Cl, 7.64; N, 9.06. Found C, 72.35; H, 3.80; Cl, 7.45; N, 9.00%.

Reaction of quinoline chalcone 19 with malononitrile
A mixture of compound **19** (0.01 mol) and malononitrile (0.015 mol) in absolute ethanol (30 mL) was refluxed for 6-7 h. The reaction was monitored by (TLC). The solvent was removed under reduced pressure, and the precipitate was crystallized from petroleum ether (60-80 ºC)and ethyl acetate to give compound **25**.

2-Amino-4-(1H-indol-3-yl)-6-(4-(((2-oxo-1,2-dihydroquinolin-3-yl)methylene)amino) phenyl)nicotinonitrile (25)

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Crystallized from petroleum ether (60-80 °C)/ethyl acetate, deep red crystals, yield: 75%, mp 166-167°C. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 12.81 (s, 1 H, NH indole, D$_2$O exchangeable), 11.79 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 8.72 (s, 1H, H-4 quinoline), 8.53 (s, 1 H, H-C=N), 8.06-7.15 (m, 14 H, Ar-H), 4.41 (s, 2H, NH$_2$). Anal. Calcd. For C$_{30}$H$_{20}$N$_6$O (480.50): C, 74.99; H, 4.20; N, 17.49. Found C, 74.87; H, 4.15; N, 17.38%.

Reaction of quinoline chalcone 21 with phenyl hydrazine

A solution of chalcone **21** (0.01 mol) and phenylhydrazine (0.015 mol) in absolute ethanol (30 ml) was refluxed for 5h. The solvent was removed under reduced pressure, and the solid product was subjected to column chromatography on silica gel using petroleum ether (60-80 °C)/ethyl acetate as an eluent to separate two products **26** and **27**.

3-(((4-(5-(4-Hydroxy-3-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenyl)imino)- methyl)quinolin-2(1H)-one (26)

Eluent: petroleum ether (60-80 °C)/ethyl acetate (90/10, *v/v*), orange crystal, yield: 25%, mp 299-301°C. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 10.14 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 8.98 (s, 1 H, H-4 quinolinone), 7.85 (s, 1 H, N=CH), 7.85-7.42 (m, 4 H quinolinone + 4 H phenyl), 7.36-7.02 (m, 3 H Ar, of 3-methoxy-4-hydroxyphenyl + 5 H phenylpyrazole), 7.00 (s, 1 H, pyrazole), 4.41 (s, 1 H, OH, D$_2$O exchangeable), 3.82 (s, 3 H, OCH$_3$). MS (EI, 70 eV): *m/z* (%) = 435 ((M$^+$-C$_6$H$_5$) 3), 342

[(M^{+1}- (C$_{10}$H$_7$N$_2$O   ), 6]. Anal. Calcd. For C$_{32}$H$_{24}$N$_4$O$_3$(512.28): C, 74.99; H, 4.72; N, 10.93. Found: C, 74.87; H, 4.66; N, 10.85.

3-(((4-(5-(4-Hydroxy-3-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)imino)methyl)quinolin-2(1H)-one (27).

Eluent: petroleum ether (60-80 °C)/ethyl acetate (85/15, *v/v*), orange crystal, yield: 43%, mp 185-186°C. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 11.79 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 7.85 (s, 1 H, N=CH), 7.78-7.13 (m, 9 H (5 H quinolinone + 4 H phenyl)), 7.05-6.70 (m, 3 H vanillin + 5 H (*N*-phenyl), 4.41 (s, 1 H, OH, D$_2$O exchangeable), 4.04- 3.73 (m, CH$_2$ and CH pyrazoline), 3.71 (s, 3 H, OCH$_3$). MS (EI, 70 eV): *m/z* (%) = 437 (M$^+$-C$_6$H$_5$), 5). Anal. Calcd. For

C$_{32}$H$_{26}$N$_4$O$_3$ (514.57): C, 74.69; H, 5.09; N, 10.89. Found: C, 74.56; H, 5.01; N, 10.81.

Formation of pyrimidine derivatives 28 and 29 from chalcones 23 and 24.

A mixture of chalcone **23** (0.01 mol) and urea (0.01 mol) was dissolved in ethanolic sodium hydroxide (10 mL, 10%). The reaction mixture was stirred about 5-6 h with magnetic stirrer. The reaction mixture was poured onto crushed ice. The precipitate isolated was filtered, washed with ethanol and recrystallized to produce quinolinone pyrimidine **28**.

*3-(((4-(2-hydroxy-6-(2-hydroxyphenyl)pyrimidin-4-yl)phenyl)imino)methyl)- quinolin-2(1H)-one (28).*

Crysallized from pet.ether (60-80 °C)/ethyl acetate, deep brown crystal, yield 60%, mp 350-351°C. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 10.37 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 8.47 (s, 1 H, N=CH), 8.14-7.15 (m, 14 H, Ar-H), 6.70 (s, 1 H, OH pyrimidine, D$_2$O exchangeable), 5.47 (s, 1 H, OH, D$_2$O exchangeable). Anal. Calcd. For C$_{26}$H$_{18}$N$_4$O$_3$(434.45): C, 71.88; H, 4.18; N, 12.90. Found: C, 71.76; H, 4.15; N, 12.84.

Reaction of quinoline chalcone 24 with thiourea

A mixture of chalcone **24** (0.01mol) and thiourea (0.01 mol) was dissolved in ethanolic sodium hydroxide (10 mL, 10 %). The reaction mixture was stirred about 6-8 h with magnetic stirrer. The reaction mixture was poured onto crushed ice. The precipitate isolated was filtered, washed with ethanol and recrystallized from ethyl acetate to afford quinolinone thiopyrimidine **29**.

3-(((4-(6-(2-chloroquinolin-3-yl)-2-thiono-1,2,3,6-tetrahydropyrimidin-4-yl)phenyl)imino)methyl)quinolin-2(1H)-one (29).

Crystallized from ethyl acetate/ petroleum ether (60-80 °C) , brown crystal, yield 63%, mp 243-244°C. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm): 8.48 (s, 1 H, NH quinolinone, D$_2$O exchangeable), 7.95 (s, 1 H, N=CH), 7.86-7.43 (m, 5H quinolinone + 4H, Ar-H), 7.40-7.14 (m, 5 H, chloroquinoline-+ H-b pyrimidine), 5.55 (d, 1 H, H-a pyrimidine), 2.89, 2.73 (2 s, 2 H, 2 NH-pyrimidine, D$_2$O exchangeable). MS

(EI, 70 eV): *m/z* (%) = 359 [(M$^+$- 163(   ),
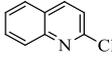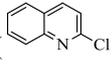
23], 329 [M$^+$-(+2NH,5), 275 (M$^+$ - (

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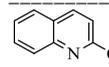
$Cl + C=S$), 3%] .   Anal. Calcd. For $C_{29}H_{20}ClN_5OS$ (522.02): C, 66.72; H, 3.86; Cl, 6.79; N, 13.42; S, 6.14 Found: C, 66.61; H, 3.81; Cl, 6.72; N, 13.35; S, 6.09.

Results and discussion

Different methods have been developed for functionalized quinoline derivatives [11-27]. 2-Chloro-3-formylquinoline (**1**) was obtained via Vilsmeier Haack reaction, and transformation of the 2-chloro and 3-formyl groups to various functionalities can afford the new quinoline derivatives [28-30]. Then, 2-oxo-3-formyl quinoline (**2**) was synthesized via hydrolytic reaction of compound **1** in the presence of 70% aqueous acetic acid solution [27]. In addition, 2-chloro-3-(hydrazonomethyl)quinoline (**8**) was produced from the reaction of compound **1** with hydrazine hydrate.

In the present study six new substituted Schiff bases **7, 9, 11, 13, 15**, and **17** were prepared in good yields from the condensation reaction of 2-oxo-3-formyl quinoline (**2**) with different primary amines namely, 2-aminothiophenol (**3**), 2-aminothiazol (**6**), 2-chloro-3-(hydrazonomethyl)quinoline (**8**), 1- (3-aminophenyl)ethanone (**10**), 4-aminophenol (**12**), 4-aminobenzoic acid (**14**), and 3-amino-2-thioxothiazolidin-4-one (*N*-aminorhodanine) (**16**) in hot ethanol. But in case of N-aminorhodanine **16**, the reaction was also performed in hot ethanol and acetic acid as a catalyst and compound **17** was obtained in a good yield [31,32] (Scheme 1).
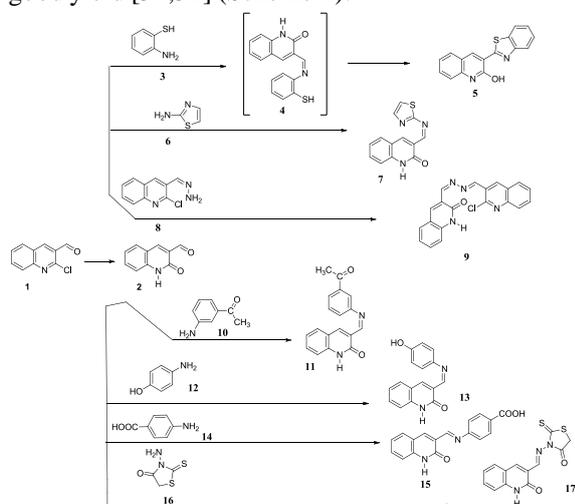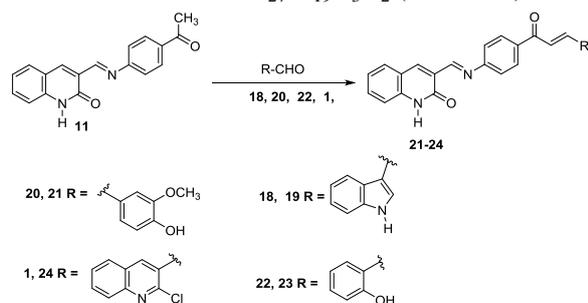

Scheme 1

We have found that the behaviour of 2-oxo-3-formyl quinoline (**2**) towards 2-aminothiophenol (**3**) in refluxing condition with ethanol, yielded firstly the intermediate Schiff base **4** which cyclizes directly through the sulphur atom to give the new five – membered ring structure namely, 3-(benzo[d]thiazol-2-yl)quinolin-2(1H)-one (**5**). Generally, Schiff base derivatives have nitrogen donor atoms, and presence of functional group like OH-or SH- close to the azomethine group assists to form a five- or six-membered ring with the metal ion [33,34]. The most significant characters in the spectroscopic data of compound **5** are the absence of SH and HC=N protons in their ¹H NMR and IR spectra and the presence of the OH proton at δ 12.50 ppm (D₂O exchangeable) and at $v = 3439$ cm^{-1}, respectively and with the identical mass spectrum, the M⁺ was found at 278 (100%).

While, the reaction of formyl quinolinone **2** with the previously mentioned amine derivatives **6, 8, 10, 12, 14** and **16** under the same experimental conditions, afforded the new compounds **7, 9, 11, 13, 15** and **17** respectively. Their elemental analyses and spectroscopic results were confirmed with the proposed structures. The structure of compound **11** was confirmed by compatible elemental analysis and spectroscopic data. The IR spectrum of 3-(((3-acetylphenyl)imino)methyl)quinolin-2(1H)-one (**11**) taken as a representative example, revealed the existence of a very strong intensity absorption band at 1489 cm^{-1} attributed to -C=N. Its ¹H NMR spectrum in DMSO exhibited signal at δ 8.47 ppm referred to azomethine proton (HC=N-), while the free NH₂ protons and the signal of aldehydic (CHO) proton are not present in the spectrum. Noteworthy in its ¹³C NMR spectrum the absence of (CO) group of aldehyde as well as the formation of (C=N-) group at δ 142.31 ppm was observed, and the MS of compound **11** the M⁺ ion peak at 290 (100%), which in accord with the expected structure. Generally, the formation of an imine involves two steps, firstly the nucleophilic attack on the carbonyl carbon of the aldehyde by amine, afforded the dipolar intermediate followed by intramolecular arrangement and formation of the unstable hydroxyl compound which on dehydration, Schiff base of compound **11** was obtained. The result of this reaction is a compound in which the carbonyl group (C=O) is replaced by (C=N) which is named an imine (Scheme 1). It is

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worth to note that degradation of Schiff base derivatives can occur during the crystallization step. Chromatography of substituted Schiff base on silica gel might result in the decomposition of the product via hydrolysis [34].

On the other hand, chalcone and its derivatives are natural biocides and are known intermediates in the preparation of heterocyclic compounds with different biological interests. Moreover, different methods are available for the preparation of chalcone derivatives. The most convenient and simple method is *Claisen-Schmidt* condensation reaction of equimolar quantities aryl methylene ketone with aryl aldeyde in the presence of alcoholic alkali [35-37]. Therefore, novel chalcone derivatives **19**, **21**, **23** and **24,** were synthesized *via* Claisen-Schmidt condensation reaction of equimolar quantities of different aldehydes namely, indol-3-aldehyde **(18)**, 4-hydroxy-3-methoxybenzaldehyde **(20)**, 2-hydroxybenzaldehyde **(22)**, and 2-chloro-3-formylquinoline **(1)** with 3-(((3-acetylphenyl)imino)methyl)quinolin-2(1H)-one **(11)**. The structures of the separated products were confirmed based on their spectral data and elemental analyses. So, compound **19** was taken as an example. It was obtained in the form of brown crystals, with identical mass spectrum. Its micro analytical data were comparable (Experimental). The ^{1}H NMR spectrum showed the absence of the signals of protons of both aldehydic group and acetyl group which exhibit are found at δ 9.05 and 2.49 ppm, respectively. Moreover, the two doublets of α- and β-ethylenic protons of compound **19** were exhibited at δ 7.23 and 7.37ppm, and showed large coupling constant (^{3}J$_{HH}$ =15.1 Hz). This features attributed to E-isomer [38]. Its MS recorded the molecular ion peak at m/z 417 (M$^+$, 2 %) which corresponded to a molecular formula of $C_{27} H_{19}N_3O_2$ (Scheme 2).

Moreover, cyanopyridine derivative **25** is prepared from the condensation reaction of quinoline chalcone **19** with malononitrile in boiling ethanol. The structure confirmation of compound **25** was supported by elemental analysis and ^{1}H MNR spectrum. The ^{1}H MNR spectrum also exhibited signals at δ 12.81 and 11.79 ppm for 2NH of indole and quinoline rings, and a singlet at δ = 8.53 ppm for -CH=N, and a singlet at δ 4.41 ppm for NH$_2$ (Scheme 3).
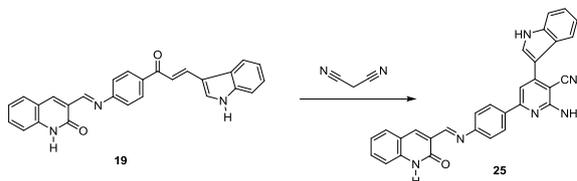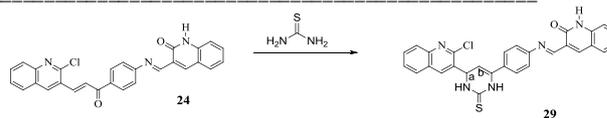
Scheme 3

Pyrazole compounds have several applications in many fields. One of the methods for the preparation of such compounds is from chalcone via the cyclization of substituted hydrazine [37]. Pyrazole compounds **26** and **27** were isolated by column chromatography, when chalcone was **21** reacted with phenyl hydrazine in ethanol, a mixture of two compounds were separated. The first compound (25%), namely 3-(((4-(5-(4-hydroxy-3-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)phenyl) imino)methyl) quinolin-2(*1H*)-one **(26)** and the second compound is (43%) 3-(((4-(5-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4,5-dihydro-*1H*-pyrazol-3-yl)phenyl)imino)methyl)- quinolin-2(*1H*)-one **(27)**. Structures of compounds **26** and **27** were confirmed by ^{1}H NMR and MS spectroscopy. The most characteristic features in their spectroscopic data is the presence of signal at δ7.00 ppm for N-C=CH in the ^{1}H NMR spectrum of pyrazole **26**, while in pyrazole **27** presence of multiplet signals at δ 4.04-3.71 ppm for CH$_2$ and CH pyrazole. Compound **27** undergoes dehydrogenation to afford product **26**, and absence of the suggested hydrazone compound (Scheme 4).

Scheme 4

Scheme 2

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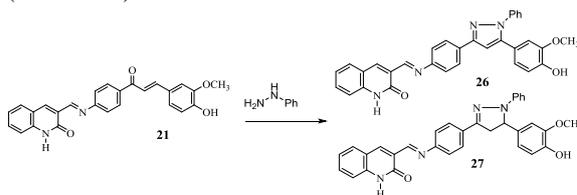
On the other hand, pyrimidine derivatives have broad spectrum of usage and its nucleus also exists in vitamin B$_2$ and folic acid. Moreover, pyrimidine heterocycles carrying hydroxyl group have a matchless place in the medicinal chemistry, and also a pivotal role in biological activities as well as synthetic drugs [39-40].Therefore, condensation of substituted quinoline chalcone derivatives **23** with urea and **24** with thiourea under basic condition produced the pyrimidine derivatives **28** and **29**. Their structures could be confirmed on the basis of
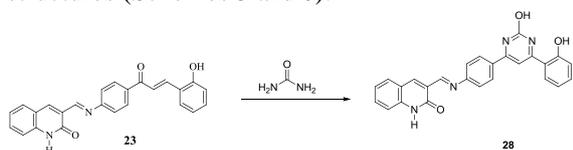

Scheme 6

Antimicrobial Evaluation

The antimicrobial activity of the tested compounds was examined *in vitro* against *Gram positive*

Table 1: The obtained results revealed that the tested compounds had different antimicrobial responses.

Organism	Gram Strain	Inhibition Clear Zone (mm) Compound No.														Reference antibiotic
		5	9	11	13	17	19	21	23	24	25	26	27	28	29	
Bacillus cereus	+ve	10	0	10	0	0	0	16	16	40	12	15	16	0	15	30
Staphylococcus aureus	+ve	0	0	0	0	0	0	0	0	10	11	21	10	16	9	30
Escherichia coli	-ve	10	0	15	0	0	0	15	0	0	20	20	12	9	12	15
Pseudomonas aeruginosa	-ve	0	0	0	0	0	10	0	0	10	15	15	12	·	0١	20
Candida albicans	Yeast	0	0	18	0	0	0	0	10	40	15	12	15	8	8	35

elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of compound **28** exhibited a singlet at δ 6.70 ppm which readily assigned to the proton of hydroxyl group of pyrimidine, and absence of 2 NH of urea. But the ^{1}H NMR spectrum of compound **29** showed signals at δ 2.89 and 2.73 ppm for 2 NH (D$_2$O exchangeable) of pyrimidine thione and at δ 5.55 ppm (d, 1H, H-a, NH-CH pyrimidine). Their mass spectra were conclusive in assigning the structures (Schemes 5 and 6).

Scheme 5

The reaction proceeds either by 1,2 or 1,4 *Michael addition* of the urea anion, *via* nucleophilic addition of the anion nitrogen of urea derivatives to the double bond of the α,β unsaturated system, followed by cyclization of the intermediate and expulsion of a molecule of water to afford pyrimidine **28** (Scheme 5) and pyrimidine thione **29** (Scheme 6).

bacteria, Bacillus cereus, Staphylococcus aureus ATCC 6538*, and Gram negative bacteria Escherichia coli* NRRN 3008, *Pseudomonas aeruginosa* ATCC 10145 and *yeast Candida albicans* EMCC105. The obtained results are compared with the reference antibiotic Cephradine that was purchased from Egyptian markets [41-44].

As shown in Table 1. Fourteen compounds were screened for their *in vitro* antimicrobial activity. Among the synthesized compounds **5**, **9, 11, 13, 17, 19, 21, 23, 24**, and **25-29**, compound **24** had superior inhibition effect against *Gram positive bacteria Bacillus cereus*, and the yeast pathogen *Candida albicans* exceeding the reference antibiotic with the inhibition clear zone diameter reached 40 mm . Compounds **25** and **26** produced also higher efficacy against *Gram negative bacteria Escherichia coli* higher than the reference drug, the clear inhibition zone reached 20 mm. Moreover, compounds **11** and **21** exhibited equal antimicrobial activity against *Gram negative bacteria E. coli* as compared to the reference antibiotic. Compounds **9, 13** and **17** are completely inert appearing no biological activity. It is worth to notice that in all readings, compound **24** yields high biological activity

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except against *Gram negative bacteria E. coli*. While compounds **25** and **26** showed high antimicrobial activity against *Gram negative bacteria   E. coli* exceeding the reference drug. However, the other synthesized compounds showed various inhibitory effects and revealed low or no antimicrobial activities.

Minimum Inhibitory Concentration (MIC):
Minimum Inhibitory Concentration (MIC) was evaluated for the most active compounds **11**, **21** and **24** against *E. coli, Bacillus cereus* and *Candida albicans* (Table 2).

Table (2): The antibacterial and antifungal activities of 11, 23 and 24

E. coli	**11**	**23**	*Bacillus cereus*	**24**	*Candida albicans.*	**24**
5 uL	0	0	5 uL	0	5 uL	0
10 uL	12	0	10 uL	10	10 uL	10
15 uL	12	0	15 uL	12	15 uL	12
20 uL	12	13	20 uL	15	20 uL	13
25 uL	12	13	25 uL	15	25 uL	13

The results obtained as shown in Table 2, revealed that MIC of compound **11** against *E. coli* is 10 μL, while it is 20 μL for compound **21** against the same bacterium (*E. coli*). On the other hand, compound **24** yielded MIC of 10 μL against the two microorganisms, *Bacillus cereus* and *Candida albicans* which is good and highly promising results.

Antimicrobial Assay
Preparation of microbial suspensions
The antibacterial and antifungal activities were carried out in the Microbial
Chemistry Department, National Research centre, using the diffusion plate method. [41-44] A filter paper sterilized disc saturated with measured quantity (25 μL) of the tested sample (1 mg/mL) is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (potato dextrose agar) which has been seeded with the spore suspension of the test organism. After incubation at 37°C for 24 h for bacteria (in case of fungi, at 25°C for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone

(cm) / plate diameter x 100). All measurements were done in DMSO as a solvent which has zero inhibition activity.

Molecular Docking
Docking studies were performed to assess the molecular affinity between the synthesized compounds and the target protein. Determination of the consistent receptor was based on previous studies. The crystallographic structure of the protein (PDBs) was produced from the protein data bank. Macromolecule file (PDB code: 3pte) was modified using the auto-dock tools (ADT) package. Compounds **5, 11, 21, 23** and **24** were studied for their affinity to the penicillin-binding proteins. All of the docking was performed by the auto-dock tools. The current docking results showed that compound **24** has the highest binding affinity (102.3 Kcal/mole) to the Penicillin-binding proteins. While compound **5** has the lowest biding affinity with 24.3 kcal/mole, which is congruent with the IC$_{50}$ values. The docking studies show that there are interactions between the compound **24** and the Asn211 residue through hydrogen bonds via the amino group. The compound binding is near the active site of the protein which suggests its potential effect. Therefore, compound **24** may have the most potential anti-bacterial activity (Figures 1 and 2).

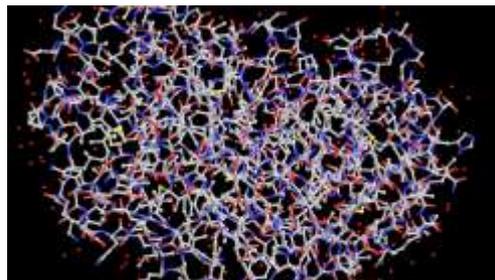*Figure (1) 3D structure of Penicillin-binding proteins (PDB ID: 3pte)*

Figure (2) Site for compound 24 binding to penicillin-binding proteins.

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Conclusions

Results of this study illustrated that the novel compounds of 2-oxoquinoline- *Schiff base* derivatives and chalcone derivatives were prepared at have been investigated for their antimicrobial interest. A simple method was presented for the preparation of substituted *Schiff base*s by condensation reaction of 3-formyl-2-quinolinone with different amines in ethanol. Moreover, four substituted chalcones have been studied, too. In addition, upon treatment of chalcone derivatives **19, 21, 23** and **24** with malononitrile, phenyl hydrazine, urea and thiourea, the corresponding cyanopyridine **25**, pyrazole **26** and **27**, and pyrimidine derivatives **28** and **29** were obtained respectively. The antimicrobial evaluation of the tested compounds was examined with various pathogenic strains of *Gram +ve bacteria*, *Gram -ve bacteria* and yeast. Compounds **11** and **21** showed equal antimicrobial activity to the reference antibiotic against *E. Coli*. Compound **24** had superior inhibition against *B. Cereus* gram +ve bacteria and the yeast pathogen *Candida albicans* exceeding the reference antibiotic. As well compounds **25** and **26** exhibited high antimicrobial activity against *Gram negative bacteria E. coli*. In addition, the others revealed different effect and showed low or no antimicrobial activities.

Acknowledgements

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