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Microwave assisted synthesis of amide derivatives of the drug ciprofloxacin and screening the biological properties

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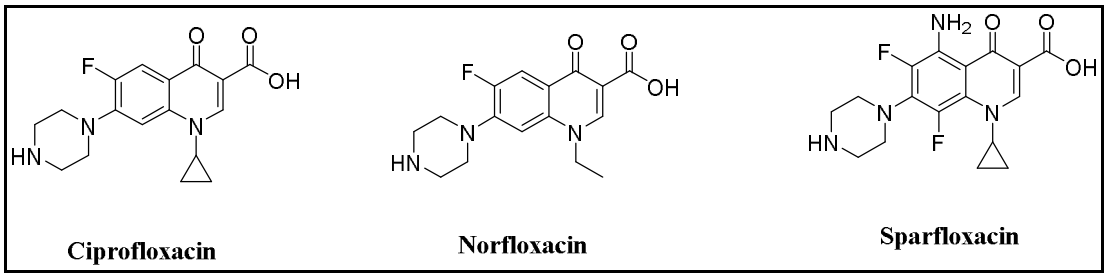
Abstract : It is synthesis of organic compounds derived from drug ciprofloxacin as amide form with the help of microwave irradiation. It created a series of these compounds **(3a-3n)** by ester derivative as intermediate. These compounds have been diagnosed using the following spectroscopic methods: IR, ^{1}HNMR and ^{13}CNMR as well as the use of elemental microanalysis (CHN) found that all spectra match the look and structural molecule. All compounds proved better effective against bacterial Gram-negative and positive like bacteria type (*Proteus mirabilis, Escherichia coli, Staphylococcus aureus, Granuticetella adiacens*).
Keywords: Antibacterial, Thiazole, Ciprofloxcin, DNA gyrase, fluoroquinolones, Amide.

1. Introduction:

Drugs that has the composition of chemical fluoroquinolones such as ciprofloxacin, norfloxacin and sparfloxacin proved highly effective and wide acceptance in various bacterial infections[1-6]. The activity derived from the inhibition of action bacterial DNA gyrase, this enzyme is responsible for DNA replication[7-11]. In addition, the deployment of the anti-containing fluoroquinolones fitted carboxyl group at the site N-1, showed as anti HIV [12].Quinolone antibiotics are used as a treatment widely because of their safety, address a wide range of bacteria and less resistance[13-16].Many of the research conducted on ciprofloxacin for the synthesis of new antibiotics, which chose the site 7 to prepare new derivatives as anti-mycobacterial activity, antibacterial and antifungal [17-24].



Amines play a key role in the pharmaceutical manufacturing process as well as in the formation of the main association in proteins, amides represent a very well-known brand drugs[25]. For example, Atorvastatin, blocks the production of cholesterol[26], Lisinopril inhibitor of angiotensin enzyme [27], Diltiazem calcium channel blocker [28], Valsartan blockade of angiotensin receptors [29]. Direct interaction between the carboxyl group and amine to prepare amides requires heating up more than 200°C to get rid of the water generated [30-32], Therefore it requires first convert the hydroxyl group to a good leaving group before adding it to the amine was to

transferred to the ester group as an intermediate and then synthesis of amines [33]. A continuation of previous work in the synthesis of new amide derivative[34], and furthermore fluoroquinolones represent best synthetic antibacterial agents [35–44], so we reported and described the synthesis of new series of fluoroquinolone amide derivatives via carboxylic group at C-3 that was esterified andsubjected to nucleophilic attack at the carbonyl carbon by different amines and screening in vitro of its antibacterial activity aims at further investigation of ciprofloxacin amides derivatives against some Gram-positive and Gram-negative bacteria.

2.Experimental

2.1. Materials and methods

All the chemical materials equipped by Sigma-Aldrich, Merck, Scharlau and Fluka company, the apparatus used in current research (Stuart) melting point (SMP30, England). UV- lamp at 254- 366 nm; Thermo- Circulator (Labtech), England. Infrared red were measured on (Shimaduz, Japan) (FT -IR)–IR Prestige-21 Spectrophotometer in Kufa University. ^{1}H- NMR Spectrophotometer (Avance III, Bruker 300 MHz) with a scale in ppm and TMS as internal standard, all ^{1}H- NMR Spectra were examined in dimethyl sulfoxide and 100 MHz ^{13}C- NMR Spectrometer in university of Toronto. Microwave oven LG MOD MH7947S 1450- 1150 W.

2.2.General procedure for preparation of amide derivatives [31]:

Synthesis of different derivatives of ciprofloxacin was attempted with equimolecular of various aromatic amines. Ciprofloxacin (0.001moles) was added to the round bottomed flask having (30 ml) of absolute ethanol, (ml) of sulphuric acid was added to the flask and the reaction was refluxed (400W, 20%) in microwave oven and irradiated about 20 min, After the depletion of ciprofloxacin and forming ciprofloxacin ester intermediate (Tested by TLC) 0.001 molar solution of aromatic amines (prepared in ethanol) were added separately and the reaction was again refluxed for about 15 min. till completion and Thin layer chromatography was used to monitor reaction. The volume of the reaction mixture was then reduced by rotary- evaporation. The precipitates were filtrated off, washed with ethanol to give compound.

2.2.1.1-cyclopropyl-6-fluoro-*N*-(3-hydroxyphenyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3a):

White, Yield: 66%, M.P.: 276 °C FT- IR (KBr cm^{-1}): 3435 ν(OH) (phenol), 1720ν(C=O) (amide), 1629 νC=O (pyridone). ^{1}H-NMR (300 MHz-DMSO-*d6-δ*, ppm): 0.67- 1.9 (m, 5H, $H_{\text{cyclopropane}}$), 2.90- 3.60 (m, 8H, $H_{\text{piperazine}}$), 4.0 (s, 1H, N-C*H*=C-C=O), 5.0 (m, 1H, N$H_{\text{piperazine}}$), 6.70- 7.90 (m, 7H, Ar-*H*) 9.03 (s,1H, C=O-N*H*), 11.01(s,1H, Ar-O*H*). ^{13}C-NMR (300 MHz-DMSO-*d6, δ*, ppm): 205 (1C, *C*=O$_{\text{pyridon}}$), 160 (1C, *C*=O-NH), 140- 134 (14C,C_{aromatic}), 104 (2C, *C=C*), 32- 36 (4C, $C_{\text{piperazine}}$), 14- 18 (3C, $C_{\text{cyclopropane}}$).Anl. calcd. for $C_{23}H_{23}FN_4O_3$: C, 65.39; H, 5.49; N, 13.26. Found: C, 65.44; H, 5.53; N, 13.20%.

2.2.2.1-cyclopropyl-6-fluoro-*N*-(4-bromophenyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3b):

White, Yield: 60%, M.P: 285 °C, FT-IR (KBr, cm^{-1}): 3516 ν(OH) (tautomerism), 3414 ν(N-H) (amide), 1720 ν(C=O) (amide), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm): 0.74- 1.76 (m, 5H, $H_{\text{cyclopropane}}$), 3.0- 4.33 (m, 8H,$H_{\text{piperazine}}$), 4.50 (s, 1H, N-C*H*=C-C=O), 5.60 (t, 1H, N$H_{\text{piperazine}}$), 6.58- 7.83 (m,7H, Ar-*H*), 9.0 (s, 1H, C=O-N*H*). ^{13}C-NMR (300 MHz, DMSO-*d6, δ*, ppm): 210 (1C,C_{pyridone}), 164 (1C, *C*=O-NH), 114- 134 (14C, C_{aromatic}), 106 (1C, *C=C*), 36 (4C,$C_{\text{piperazine}}$), 16 (3C, $C_{\text{cyclopropane}}$).Anl. calcd. for $C_{23}H_{22}BrFN_4O_2$:C, 56.92; H, 4.57; N, 11.54. Found: C, 56.99; H, 4.60; N, 11.50%.

2.2.3.1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-*N*-(pyridin-2-yl)-1,4-dihydroquinoline-3-carboxamide (3c):

White, Yield: 72%, M.P.: 272 °C, FT- IR (KBr, cm^{-1}): 3417 ν(N-H) (amide), 1720 ν(C=O) (amide), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm): 0.94- 1.86 (m,5H, $H_{\text{cyclopropane}}$), 2.4- 2.7 (m, 8H,$H_{\text{piperazine}}$), 4.50 (s, 1H, N-C*H*=C-C=O), 5.03- 5.99 (t, 1H, N$H_{\text{piperazine}}$), 7.01- 7.63 (m,7H, Ar-*H*), 9.0 (s, 1H, C=O-N*H*). Anl. calcd. for $C_{22}H_{22}FN_5O_2$:C, 64.85; H, 5.44; N, 17.19. Found: C, 64.95; H, 5.49; N, 17.22%.

2.2.4.1-cyclopropyl-6-fluoro-*N*-(4-methoxyphenyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3d):

White, Yield 75%, M.P.: 279 °C, FT-IR (KBr, cm^{-1}) 3437ν(N-H+ OH) (amide+ carboxylic acid), 1728ν(C=O) (amide), 1666ν(C=N), 1627 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ,* ppm): 0.9-1.02 (m, 5H, $H_{cyclopropane}$), 2.60- 2.90 (m, 8H, $H_{piperazine}$) 3.86 (s, 3H,O-C*H3*), 3.96 (s, 1H, N-C*H*=C-C=O), 4.62 (br, 1H, O*H*-C=$N_{tautomerism}$), 6.22- 7.87 (m,7H, $H_{aromatic}$), 9.36 (s, 1H, C=O-N*H*), ^{13}C-NMR (300MHz, DMSO-*d6, δ*, ppm): 215 (1C,$C_{pyridone}$), 165 (1C, *C*=O-NH), 114- 134 (14C, $C_{aromatic}$) 102 (2C*, C=C)*, 80 (1C, O*C*H3), 18- 22 (3C, $C_{cyclopropane}$). Anl. calcd. for $C_{24}H_{25}FN_4O_3$: C, 66.04; H, 5.77; N. 12.84, Found: C, 66.02; H, 5.67; N, 12.88%.

2.2.5.4-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamido) benzoic acid (3e):

White, Yield: 62%, MP.: 274 °C, FT-IR (KBr cm^{-1}): 3435 ν(N-H+ OH) (amide+ carboxylic acid), 1720ν(C=O) (amide), 1629 ν C=O (pyridone), 1271 ν(OH) (OH bending vibration carboxylic acid). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm), 1.40- 1.58 (m, 5H*,* $H_{cyclopropane}$), 2.48- 2.84 (d, 4H, $H_{piperazine}$), 5.08 (br, 1H, O*H*-C=$N_{tautomerism}$), 6.62- 7.84 (m,7H, Ar-*H*), 9.41 (s, 1H, C=O-N*H*), 13.28 (s, 1H, COO*H*). 13C-NMR- MHz, DMSO- *d6, δ*, ppm): 205 (1C, $C_{pyridone}$), 190 (1C, *C*OOH), 168 (1C, *C*=O-NH), 118- 135 (14C, $C_{aromatic}$), 104-106 (2C, C=C), 12- 16 (3C, $C_{cyclopropane}$), 34- 36 (4C, $C_{piperazin}$). Anl. calcd. for $C_{24}H_{23}FN_4O_4$: C, 63.99; H, 5.15; N, 12.44. Found: C, 63.90; H, 5.10; N, 12.40%.

2.2.6.1-cyclopropyl-6-fluoro-*N*-(2-hydroxyphenyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3f):

White, Yield: 68%, M.P.: 278 °C, FT- IR (KBr, cm^{-1}), 3437 ν(OH) (Phenol), 1718ν(C=O) (amide), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz-DMSO-*d6, δ*, ppm): 0.8- 1.4 (m, 5H, $H_{cyclopropane}$), 2.5- 3.47 (m, 8H, N-CH_2-CH_2-N), 3.94 (s, 1H, N-C*H*=C-C=O), 5.0 (s, 1H, $H_{piperazine}$), 7.72- 7.80 (m, 7H, Ar-*H*), 9.0 (s, 1H, C=O-N*H*), 11.0 (s, 1H, O*H*). ^{13}C-NMR (300 MHz-DMSO-*d6, δ*, ppm): 205 (1C, $C_{pyridone}$), 160 (1C, *C*=O-NH), 140- 134(14C, $C_{aromatic}$), 104 (2C, *C=C*), 32- 36 (4C, $C_{piperazine}$), 14- 18 (3C, $C_{cyclopropane}$). Anl. calcd. for $C_{23}H_{23}FN_4O_3$: C, 65.39; H, 5.49; N, 13.26. Found: C, 65.48; H, 5.50; N, 13.22%

2.2.7.1-cyclopropyl-6-fluoro-*N*-(4-hydroxyphenethyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3g):

White, Yield: 73%, M.P.: 282 °C, FT-IR (KBr, cm^{-1}): 3437 ν(NH+ OH) (amide+ phenol), 1718 ν(C=O) (amide), 1664ν(C=$N_{tautomerism}$), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz-DMSO-*d6, δ*, ppm), 0.8-1.70 (m, 5H, $H_{cyclopropane}$), 1.80- 2.30 (m, 8H, $H_{piperazine}$), 3.10- 3.90 (m, 4H, N-C*H2*-C*H2*-N), 5.0 (s, 1H, N$H_{piperazine}$), 6.90- 7.80 (m, 7H, Ar-*H*), 9.2 (s, 1H, C=O-N*H*), 11.01(s, 1H, Ar-O*H*). ^{13}C-NMR 300 MHZ-DMSO-*d6, δ*, ppm): 215 (1C, $C_{pyridone}$), 165 (1C, *C*=O-NH), 116- 135 (14C, $C_{aromatic}$), 115 (2C, *C=C*), 34- 38 (4C, $C_{piperazine}$), 12 (3C, $C_{cyclopropane}$), 22 (2C, NH-*C*H_2-*C*H_2-N), 96.0(1C, C=$N_{tautomerism}$). Anl. calcd. for $C_{25}H_{27}FN_4O_3$: C, 66.65; H, 6.04; N, 12.44. Found: C, 66.69; H, 6.09; N, 12.49%.

2.2.8.4-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamido) butanoic acid (3h):

White, yield: 76%, M.P.: 268 °C, FT- IR (KBr, cm^{-1}): 3439 ν(O-H) (carboxylic acid), 1718 ν(C=O) (amide), 1629ν(C=O) (pyridone), 1271 ν(OH) (OH bending vibration carboxylic acid). ^{1}H- NMR (300 MHz-DMSO-*d6, δ*, ppm), 1.0- 1.58 (m, 5H, $H_{cycloprpane}$), 2.48- 2.84(m, 4H, N-CH_2-CH_2-N), 3.21- 3.40 (N-CH_2-CH_2-CH_2-COO), 4.32 (s, 1H, N-C*H*=C-C=O), 5.08 (s, 1H, $NH_{piperazine}$), 7.07- 7.84 (m, 3H, Ar-*H*), 9.11(s, 1H, C=O-N*H*), 13.23 (s,1H, COO*H*). ^{13}C-NMR 300 MHz-DMSO-*d6, δ*, ppm): 215 (1C, $C_{pyridone}$), 190 (1 C, *C*OOH) ,160 (1C*, C*=O-NH), 115- 135 (8C, $C_{aromatic}$), 100 (2C, *C=C*), 32- 38 (4C, $C_{piperazine}$), 20- 22 (3C, -*C*H2*C*H2*C*H2-), 14- 16 (3C, $C_{cyclopropane}$). Anl. calcd. for$C_{20}H_{23}FN_4O_4$: C, 59.69; H, 5.76; N, 13.92. Found: C, 59.65; H, 5.796; N, 13.89%.

2.2.9.*N*-(4-(benzo[d]thiazol-2-yl)phenyl)-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3i):

Pink, Yield: 68%, M.P.: 286 °C,FT- IR (KBr, cm^{-1}) 3435 ν(NH) (amide), 3238 ν(OH) (tautomerism), 1716 ν(C=O) (amide), 1668 ν(C=N) (tautomerisum), 1625 ν(C=O) (pyridon), 1525 ν(C=S) (hetero cyclic ring).1H-NMR (300 MHz-DMSO-*d6, δ*, ppm): 1.0- 1.40 (m, 5H, $H_{cyclopropane}$), 2.70- 3.50 (m, 4H, N-C*H2*-C*H2*-N), 3.90 (s, 1H, N-C*H*=C-C=O), 5.10 (s, 1H, N$H_{piperazine}$), 6.51-7.94 (s, 1H, N$H_{benzothizole}$), 9.65(s, 1H, C=O-N*H*). ^{13}C-NMR (300MH2-DMSO-*d6, δ*, ppm: 205 (1C, $C_{pyridone}$), 160 (1C, *C*=O-NH), 145 (1C, *C*=N), 118- 132 (13C, $C_{aromatic}$), 105 (2C, *C=C*), 30- 34 (4C, $C_{piperazine}$), 9- 12 (3C, $C_{cyclopropane}$). Anl. calcd. for $C_{30}H_{26}FN_5O_2S$: C, 66.77; H, 4.86; N, 12.98. Found: C, 66.79; H, 4.88; N, 13.00%.

2.2.10.1-cyclopropyl-6-fluoro-*N*-(4-nitrophenyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3j):

Yellow, Yield: 58%, M.p.: 279 °C, FT-IR (KBr, cm^{-1}): 3433 ν(N-H) (amide), 3213 ν(OH) (tautomerism), 1718 ν(C=O) (amide), 1625 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz-DMSO- *d6- δ*, ppm: 0.70-1.20 (m,5H, $H_{cyclopropane}$), 2.70- 3.90 (m, 8H, $H_{Piperazin}$), 4.10 (s, 1H, N-C*H*=C-C=O), 5.05 (m, 1H, N$H_{piperazine}$) 6.90- 7.67 (m, 7H, Ar-*H*), 9.10(s, 1H, C=O-N*H*). ^{13}C-NMR – 300 MHZ, DMSO-*d6, δ*, ppm): 215 (1C, $C_{pyridone}$), 168 (1C, *C*=O-NH), 108 (2C, *C=C*), 118- 135 (14C, $C_{aromatic}$), 30- 34 (4C, $C_{piperazine}$), 12- 14 (3C, $C_{cyclopropane}$). Anl. calcd. for$C_{23}H_{22}FN_5O_4$: C, 61.19; H, 4.91; N, 15.51. Found: C, 61.25; H, 4.93; N, 15.50

2.2.11.1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-*N*-(pyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxamide (3k):

White, Yield: 69%, M.P.: 277 °C, FT- IR (KBr, cm^{-1}): 3435 ν(N-H) (amide), 1720 ν(C=O) (amide), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm): 1.0-1.04 (m, 4H, $H_{cyclopropane}$), 2.7-3.5 (m, 8H, $H_{piperazine}$), 3.90 (s, 1H, N-C*H*=C-C=O), 5.10 (m, 1H, N$H_{piperazine}$) 6.51- 7.94 (m, 6H, $H_{aromatic\ \&benzothiazole}$), 9.65 (s, 1H, C=O-N*H*). ^{13}C-NMR – 300MHz, DMSO-*d6, δ*, ppm: 200 (1C, *C*=O). 192 (1C, *C*=O-NH), 146 (1C, *C*=N), 118- 130 (1C, $C_{pyridone}$), 104 (2C, *C=C*), 97 (1C, OH-*C*=$N_{tautomerism}$), 34- 38 (4C, $C_{piperazine}$), 12- 15 (3C, $C_{cyclopropane}$). Anl. calcd. for$C_{21}H_{21}FN_6O_2$: C, 61.76; H, 5.18; N, 20.58.

Fouund: C, 61.77; H, 5.20; N, 20.56%.

2.2.12.*N*-(2-chlorophenyl)-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3l):

Yellow, Yield: 84%, M.P.: 281 °C, FT-IR (KBr, cm^{-1}): 3435 ν(N-H+ OH) (amide+ O-H tautomerism), 1720 ν(C=O) (amide), 1666 ν(C=N) (tautomerism), 1629 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm): 0.74- 1.17 (m,5H, $H_{cyclopropane}$), 2.90- 3.90 (m, 8H,$H_{piperazine}$), 4.0 (s, 1H, N-C*H*=C-C=O), 5.0 (t, 1H, N$H_{piperazine}$), 7.0- 7.90 (m,7H, Ar-*H*), 9.10 (s, 1H, C=O-N*H*). ^{13}C-NMR (300 MHz, DMSO-*d6, δ*, ppm): 215 (1C,$C_{pyridone}$), 165 (1C, *C*=O-NH), 112- 134 (14C, $C_{aromatic}$), 108 (1C, *C=C*), 36 (4C,$C_{piperazine}$), 15 (3C, $C_{cyclopropane}$). Anl. calcd. for$C_{23}H_{22}ClFN_4O_2$: C, 62.66; H, 5.03; N, 12.71. Found: C, 62.64; H, 5.06; N,12.65%.

2.2.13.1-cyclopropyl-6-fluoro-*N*-(2-methoxyphenyl)-4-oxo-7-(piperazin-1-yl)-1,4-Dihydroquinoline-3-carboxamide (3m):

White, Yield: 74%, M.P.: 284 °C, FT- IR (KBr, cm^{-1}), 3435ν(N-H+ OH) (amide+ carboxylic acid), 1730ν(C=O) (amide), 1664ν(C=N), 1627 ν(C=O) (pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ,* ppm): 0.92-1.04 (m, 5H, $H_{cyclopropane}$), 2.61-2.92 (m, 8H, $H_{piperazine}$) 3.88 (s, 3H,O-C*H3*), 3.98 (s, 1H, N-C*H*=C-C=O), 4.62 (br, 1H, O*H*-C=$N_{tautomerism}$), 6.24- 7.89 (m,7H, $H_{aromatic}$), 9.36 (s, 1H, C=O-N*H*), ^{13}C-NMR (300MHz, DMSO-*d6, δ*, ppm): 210 (1C,$C_{pyridone}$), 165 (1C, *C*=O-NH), 114- 132 (14C, $C_{aromatic}$) 102 (2C, *C=C)*, 82 (1C, O*C*H3), 18- 24 (3C, $C_{cyclopropane}$). Anl. calcd. for $C_{24}H_{25}FN_4O_3$: C, 66.04; H, 5.77; N, 12.84. Found: C, 66.02; H, 5.67; N, 12.88%.

2.2.14.*N*-(2-bromophenyl)-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (3n):

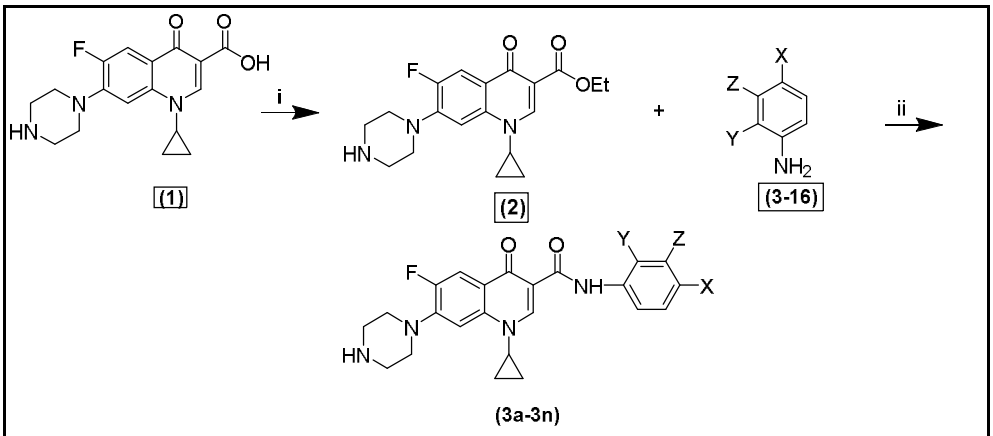
Brown, Yield 60%, M.P: 277 °C, FT- IR (KBr cm^{-1}): 3516 ν($OH_{totomerzium}$), 3414 νN-H(amide), 1720 νC=O(amide), 1629 νC=O(pyridone). ^{1}H-NMR (300 MHz, DMSO-*d6, δ*, ppm): 0.76- 1.75 (m, 5H, $H_{cyclopropane}$), 3.89- 4.23 (m, 8H,$H_{piperazine}$), 4.55 (s, 1H, N-C*H*=C-C=O), 5.61 (t, 1H, N$H_{piperazine}$), 6.58- 7.78 (m,7H, Ar-*H*), 9.0 (s, 1H, C=O-N*H*). ^{13}C-NMR (300 MHz, DMSO-*d6, δ*, ppm): 212 (1C,$C_{pyridone}$), 165 (1C, *C*=O-NH), 116- 136 (14C, $C_{aromatic}$), 108 (1C, *C=C*), 36 (4C,$C_{piperazine}$), 17 (3C, $C_{cyclopropane}$).Anl. calcd. for $C_{23}H_{22}BrFN_4O_2$:C, 56.92; H, 4.57; N, 11.54. Found: C, 56.90; H, 4.62; N, 11.49%.

2.3. Antibacterial activity assay: [33]

An antibacterial activity has been conducted according to piercing method, all ciprofloxacin amide derivatives **3a- 3n** were tested by this method against four types of bacteria gram negative such as *Escherichiacoli, Proteus mirabilis* and gram positive like *Staphylococcus aureus, Granuticetellaadiacens*. All derivatives were dissolved in (3) dissimilar concentration 0.01 gm, 0.005 gm, 0.001 gm in 10 ml of water, the surface of solid culture media (Nutrient Agar) dried and applied on the plates which had been streaked with standardized bacterial inoculums and incubated at 37 °C for 24h. This technique is based on the determination of an inhibited zone (in mm) proportional to the bacteria in the plates and the results were compared with the antibacterial activity of ciprofloxacin drug.

3. Results and discussion

Potential activity of the ciprofloxacin **1** for treatment of different strains of Gram positive and Gram negative organism prompted us to introduce much more amine groups to prepared amide, aiming to develop a new compounds having novel properties.



Amine: **3** X=H, Y=H, Z=OH
4 X=Br, Y=H, Z=H
5 pyridin-2-amine
6 X=OMe, Y=H, Z=H
7 X=COOH, Y=H, Z=H
8X=H, Y=H, Z=OH
9 4-(2-aminoethyl)phenol
10 4-(3-aminopropyl)benzoic acid
11 benzo[*d*]thiazol-2-amine
12 X=NO2, Y=H, Z=H
13 pyrimidin-2-amine
14 X=H, Y=Cl, Z=H
15 X=H, Y=OMe, Z=H
16X=H, Y=Br, Z=H

Amide:**3a** X=H, Y=H, Z=OH
3b X=Br, Y=H, Z=H
3c pyridin-2-amine
3d X=OMe, Y=H, Z=H
3e X=COOH, Y=H, Z=H
3 fX=H, Y=H, Z=OH
3g 4-(2-aminoethyl)phenol
3h 4-(3-aminopropyl)benzoic acid
3i benzo[*d*]thiazol-2-amine
3j X=NO2, Y=H, Z=H
3k pyrimidin-2-amine
3l X=H, Y=Cl, Z=H
3m X=H, Y=OMe, Z=H
3n H, Y=Br, Z=H

Scheme 1. Reagents and conditions: (i) absolute Et-OH, 5ml conc. H2SO4, reflux MWI 20 min. (ii) ethanol, Ar or aliphatic amine, reflux MWI 15-20min.

Therefore, treatment of ciprofloxacin **1** with absolute ethanol alcohol with catalytic amount of concentration sulphuric acid to synthesis ester **2** as intermediate after 20 minutes irradiated by microwave, following the reaction mixture by (TLC) when completion the reaction and consumption of ciprofloxacin forming the ester as intermediate, added the aromatic or aliphatic amine **3a- 3n** and reflux by microwave

irradiation for about 15-20 minutes. All synthesis amide compounds **3a- 3n** were washed by (ethanol: chloroform) 2:8 after evaporation by rotary evaporator yielded from (58-84) % (scheme 1).

In IR spectra noticed the absence of the band at ν = 3527 cm^{-1} OH group for carboxylic acid and presence the absorption band ν= 3200- 3414 cm^{-1} for NH vibration of amide group only amide derivate **3a, 3f and 3g** containing OH group as substituted in aromatic ring of amide were give absorption band of aromatic OH in the same region, the carboxylic C=O absorption band ν=1707cm^{-1} was shifted to ν=1720 $cm^{-1}$for amide formation, indicating the consumption of carboxylate groupin ester and amide formation as in figure 1.

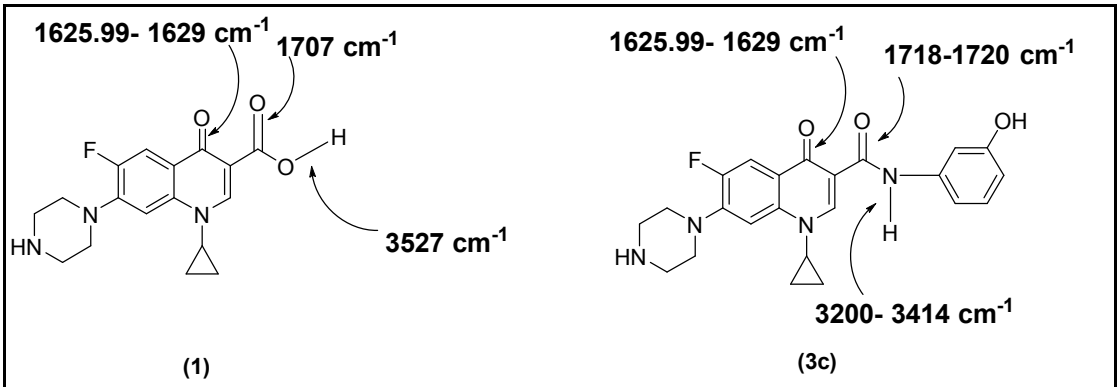


Fig 1. Compartion between **1, 3c** in IR absoption vibration band and their structures carboxyic acid and amide

In ^{1}H NMRlikewise, in IR spectra the absence of resonance of acidic proton at□ =11.02 ppm in ciprofloxacin, all amide derivatives showed a singlet signals in the region □ =9.0- 9.65 ppm, the difference in chemical shift of all synthesis compounds showed a significant □ =0.65 ppm. All other protonspractically remained same as in original molecule (ciprofloxacin), further signals back to the chemical structures as in spectral date. But ^{13}C NMR of all synthesis compounds exhibited a clear signal between □ =160- 186 ppm for carbon of amide for aromatic derivative except compound **3h** showed this signal in □ =192 ppm because for its aliphatic amide derivative, there is no significant difference in the chemical shift of carbon of carbonyl in pyridone its between □ =205- 215 ppm according to their structure. All these date were confirmed the structures of synthesized amide as well as the micro elemental analysis (CHN) fitted these compounds.

However, Figure 2 shows the resonances of carbon for carbonyl amide of compounds **3a** in comparison with compound **3b**. The resonance of carbonyl carbon (pyridone) ring of **3a** and **3b** in the not at same region at □ =205 and 215 ppm respectively shifted ~ 5 ppm, whereas the resonance of carbon of These shifts in the ^{13}C NMR resonances are indicative of the tautomeric effects form and confirmed by 1H NMR when the shifts between **3a** and **3b** was ~ 4.41 ppm, as explain in this figure 2.

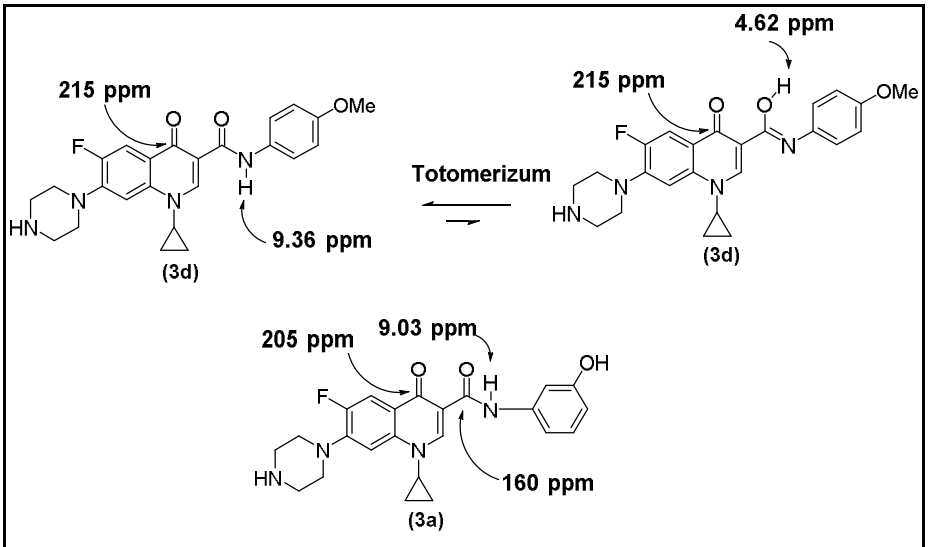


Fig 2. Resonance of carbon in 13C NMR and protons in ^{1}H NMR compartion between **3d, 3a** and the totomerisum strctures of **3a**

Antibacterial activity was determined by measuring the inhibition zone in mm, the preliminary result show the increasing of the inhibition zone when increasing the concentration of all compounds with all type of bacteria table 1. The results showed that compound **3i** was the most effective and highest activity against all types of bacteria because this compound contains has a thiazole heterocyclic ring. In particular, compounds **3a, 3f** and **3g** were found to be respectable activity against gram- negative (*E. coli*, *proteus mirabilis*) because it contains OH groups in different positions. The compounds **3a, 3l** and **3m** derivatives exhibited better activity against *Staphylococcus aureus* and *Granticetellaadiaceus*because the compounds containing bromine and chlorine atoms substituted in the phenyl ring. compounds **3e** and **3f** showed decrease in their activity against all tested bacteria. Moreover, compounds **3d** and **3m** derivatives exhibited excellent activity towards *E. coli* and *proteus mirabilis* bacteria for containing methoxy group substituted in the phenyl ring, so these excellent results suggested us to synthesis new derivatives to further study.

Table 1. Zone inhibition (mm) of ciprofloxacin and their Amide derivatives (3a-3n) against various microorganisms.

Inhibition zone (mm)												Conc µg/L			
Proteus mirabilis			Escherichia Coli			Granuticetella adiacens			Staphylococcus Aureus						
11	16	12	14	22	25	9	13	15	11	14	16	1	0.5	0.1	**3a**
12	15	19	13	15	19	15	18	21	9	12	20	1	0.5	0.1	**3b**
12	19	22	14	18	28	11	15	17	`13	14	17	1	0.5	0.1	**3c**
15	20	27	15	19	26	10	13	20	10	11	24	1	0.5	0.1	**3d**
13	15	18	11	14	17	15	19	16	10	12	14	1	0.5	0.1	**3e**
14	20	24	15	19	26	17	18	21	8	10	16	1	0.5	0.1	**3f**
16	22	26	18	25	30	10	12	14	12	16	18	1	0.5	0.1	**3g**
10	15	17	10	14	18	12	17	22	9	12	17	1	0.5	0.1	**3h**
16	24	32	18	22	30	18	21	30	12	18	26	1	0.5	0.1	**3i**
14	19	29	15	19	26	14	17	19	10	14	16	1	0.5	0.1	**3j**
20	25	30	18	20	29	12	17	22	13	16	22	1	0.5	0.1	**3k**
14	25	18	12	16	17	11	14	21	10	16	30	1	0.5	0.1	**3l**
15	20	18	13	18	19	12	16	24	10	14	28	1	0.5	0.1	**3m**
18	20	25	18	24	30	11	14	21	15	18	20	1	0.5	0.1	**3n**
11	13	17	8	11	14	9	10	12	8	10	13	1	0.5	0.1	Cip

Conclusions

The development of antibiotics for bacterial pathogenesis has a special importance in the treatment of infection diseases. The important conclusion is that the biological effectiveness of the best in the compound **3i** and **3k**, because their constituents containing organic heterocyclic rings. All of these compounds showed high effective even at low concentrations. The results also showed that all compounds are effectively much higher than the effectiveness of ciprofloxacin. Many compounds like **3e**, **3g**, **3i**, **3k**, **3l** and **3m** are a promising agent for further structural modification and pharmacological evaluation as target treatment of infections caused by these types of bacteria.

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